The New England
Journal of Medicine

Copyright, 1949, by the Massachusetts Medical Society

Volume 240 APRIL 21, 1949 Number 16

CARDIAC ANEURYSM*

MAX CAPLAN, M.D.,† AND PAUL M. SHERWOOD, M.D.‡

ROCKY HILL, CONNECTICUT

PRIOR to 1931, the diagnosis of acquired aneurysm of the left ventricle was made only ten times ante mortem.[1, 2] With the better appreciation of the significance of the clinical features of this condition and the increased use of modern diagnostic facilities, more and more cases have been reported in the literature, and a new evaluation of the prognosis is warranted. Thus, although in Parkinson, Bedford, and Thomson's[3] cases, the longest survival was thirty months, in Dressler and Pfeiffer's[4] cases it was seven years. Young and Schwedel[5] have reported the case of a patient who survived for ten years after the diagnosis of cardiac aneurysm, and Penner and Peters[6] described a patient who, up to 1946, had already survived fifteen years. Many cases have been reported in which the patients have pursued a useful and comparatively active life for two, four, five,[3] seven[4, 7] and nine[7] years after the development of the characteristic radiographic findings of ventricular aneurysm. The longest survival mentioned in the literature is a patient, followed by Robertson[8] for eighteen years, who still engages in heavy work. Formerly a rare condition, ventricular aneurysm is now frequently suspected before death and no longer, by itself, has the dire prognosis commonly associated with it in the past.[3, 9] We report herewith 2 cases of cardiac aneurysm followed on the Medical Service of the Veterans Home and Hospital at Rocky Hill, Connecticut.

CASE REPORTS

CASE 1. W. C., a 56-year-old man, was transferred to the hospital for convalescent hospital care. He was a highway-department maintenance worker, and his duties had included pick and shovel work as well as clearing snow. From 1943 to 1946 he had noted occasional sharp stabbing nonradiating pains in the anterior portion of the chest deep behind the lower third of the sternum. The onset was sudden and usually occurred while he was at work; the pain waxed and waned and varied in duration from several hours to an entire day. On the evening of June 20, 1946, he was suddenly seized with severe substernal and precordial pain, which radiated down both arms. He was immediately sent to a hospital. Two weeks later, and again 4 weeks later, while in the hospital, he had a similar but much milder episode of substernal pain. Thereafter he improved uneventfully and was transferred to this hospital.

Physical examination revealed a well developed and well nourished man who was not acutely ill. Examination of the head was not significant. The thyroid gland was not enlarged. The lungs were clear. The maximum cardiac impulse was heaving and appeared in the fourth interspace just medial to and below the left nipple and 2 cm. inside the left border of cardiac dullness. The heart sounds were distant and faint, and not in keeping with such a marked cardiac pulsation. Rhythm was regular, and no murmurs were present. The liver was not enlarged, and there was no peripheral edema.

The blood pressure was 136/84 in both arms.

Laboratory examination revealed normal urine specimens and no anemia or leukocytosis; the nonprotein nitrogen was 29, and the fasting blood sugar 103 mg. per 100 cc. and the sedimentation rate was 12 mm. per hour (Cutler method). Blood Wassermann and Mazzini tests were negative.

X-ray examination of the chest disclosed the heart to be somewhat enlarged in the transverse diameter and revealed a marked prominence and dilatation of the left border of the heart (Fig. 1). Under the fluoroscopic screen, an expanding pulsation of the bulging area that coincided with each contraction of the left ventricle was noted.

An electrocardiogram (Fig. 2) showed regular sinus rhythm, with a rate of 80, a PR interval of 0.20 second and QRS complexes of 0.08. In Lead 1 the main deflection was downward, with elevated, bowed ST segments and a shallow, inverted T wave. The R wave was notched and the T wave, low and upright in Lead 2. Lead 3 showed depressed ST segments. In the left-arm lead the main deflection was downward, with elevated, bowed ST segments, and a shallow, inverted T wave. The right-arm lead had an inverted P wave, upright QRS complexes and a diaphasic T wave. In the left-leg lead the QRS complexes and T wave were upright. The R waves were low in Lead V_1 and absent in Leads V_2, V_3, V_4 and V_5; the ST segments were elevated in Leads V_2, V_3, V_4 and V_5, and the T waves were diphasic in Lead V_2 and inverted in Leads V_3, V_4 and V_5. In Lead V_6 there were low-voltage QRS complexes, elevated ST segments and an inverted T wave. Serial electrocardiograms showed no essential change.

The patient has been fully ambulatory in the hospital and has cared for himself completely. He walks to the dining room and to the auditorium for motion-picture entertainment. He performs light work at the Department of Occupational Therapy. In addition, he voluntarily helps in small tasks about the ward. His complaints referable to the cardiovascular system are limited to palpitation after infrequent climbing of stairs. Repeated x-ray films over the two-year period while he has been in this hospital have revealed no change in the size or configuration of the heart (Fig. 1).

CASE 2. A. S., a 74-year-old man, was admitted to the hospital on July 9, 1948, because of shortness of breath. Nine months before admission, directly after arising from bed, he had suddenly been seized with excruciating pain in the left anterior portion of the chest. There was associated sweating and marked shortness of breath. He entered another hospital, where on the following day the precordial pain was more pronounced. His pulse was stated to be rapid

*From the Medical Service, Veterans Home and Hospital.

†Attending physician, Veterans Home and Hospital; chief of medicine, Meriden Hospital, Meriden, Connecticut.

‡Staff physician, Veterans Home and Hospital.

and weak, and his temperature rose to 103.6°. The white-cell count was 16,800 and an electrocardiogram showed "myocardial damage, coronary closure, and sinus tachycardia." He had severe anginal pain when moved. He gradually improved and was discharged in February, 1948. He was rehospitalized 1 month later for congestive failure and improved on digitalization. At this time x-ray films were interpreted as showing "cardiac enlargement with a question of aneurysm." He was discharged to a convalescent home in April, 1948. In July the patient was admitted to this hospital. His dyspnea had returned and was becoming progressively worse. His appetite was poor, and nocturia was present.

Physical examination revealed an elderly man in no acute distress. The fundi were Grade I and hypertensive-arteriosclerotic. The thyroid gland was not enlarged. There was no distention of the neck veins. There were scattered crepitant rales at both lung bases. The point of maximal impulse was diffuse and forceful but displaced above the left nipple and inside the midclavicular line. The heart sounds were distant. The rhythm was regular, and no murmurs

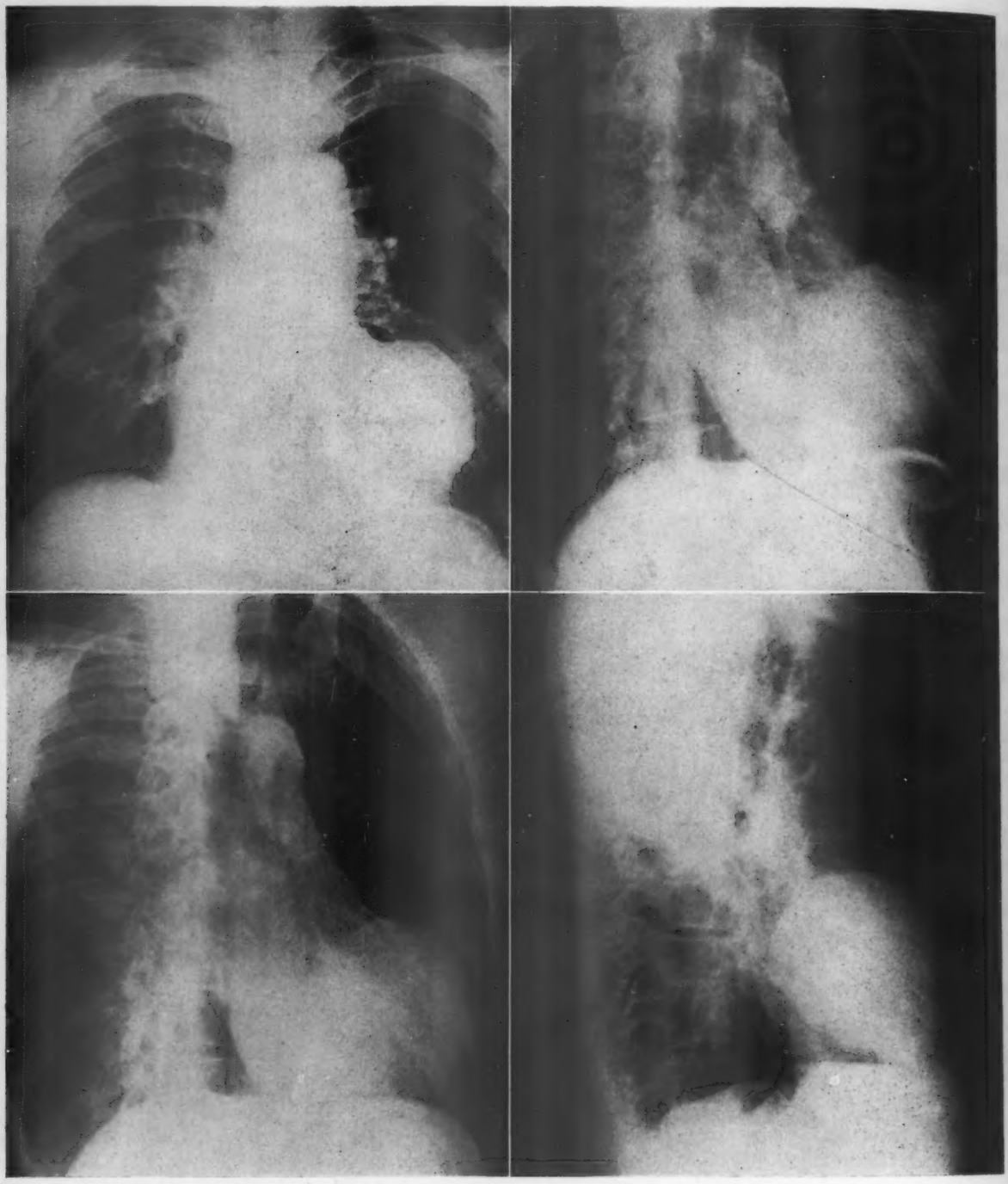

FIGURE 1. *Roentgenograms in Case 1.*

The left upper photograph shows the anteroposterior view, the right upper the right oblique view (taken in November, 1946); the left lower the right oblique view (taken in March, 1948), and the right lower the left lateral view.

were heard. The blood pressure in both arms was 150/90. The liver was enlarged and tender, and pitting edema of both ankles was present.

Laboratory examination disclosed negative urinalyses and no anemia or leukocytosis. The blood Mazzini test was negative.

X-ray examination of the chest revealed considerable cardiac enlargement. Projecting upward from the left ventricular contour there was a bulge extending for a distance of approximately 4 cm. The base of the bulge measured 8 cm. in diameter (Fig. 3).

An electrocardiogram (Fig. 4) showed regular sinus rhythm, with a rate of 94, a PR interval of 0.18 second and QRS complexes of 0.10. The Q wave was deep in Lead 1. The R waves were tall in Leads 1, 2 and 3. The ST segments were elevated in Lead 1, slightly depressed in Lead 2 and depressed in Lead 3. The T waves were inverted in Lead 1 and upright in Leads 2 and 3. The S waves were deep in Leads 2 and 3. The left-arm lead showed a deep Q wave, tall R wave, elevated ST segments and inverted T wave, and the right-arm lead small QS complex (main deflection downward) and upright T wave. The left-leg lead showed a tall R wave, deep S wave, depressed ST segments and upright T wave. Lead V_1 showed a small R wave, deep S wave and upright T wave, with U wave present, Lead V_2 showed deep QS complex and upright T wave, with U wave present. In Lead V_3 the QS complex was present, with embryonal R wave and upright T wave. In Lead V_4 the QS complex was present, with embryonal R wave, elevated ST segments and diphasic T wave. In Lead V_5 the Q wave was small, the ST segments elevated, and the T wave diphasic. The ST segments were elevated and bowed in Lead V_6, with a shallow, inverted T wave.

On a low-salt diet, digitalization, and mercurial diuretics, the patient rapidly improved and has become asymptomatic. The rales and peripheral edema disappeared, and the liver is no longer palpable. He is fully ambulatory in the hospital and is employed by the Department of Rehabilitation as an elevator operator. He has been entirely asymptomatic except for a transient episode of faintness, which occurred after he had climbed a flight of stairs.

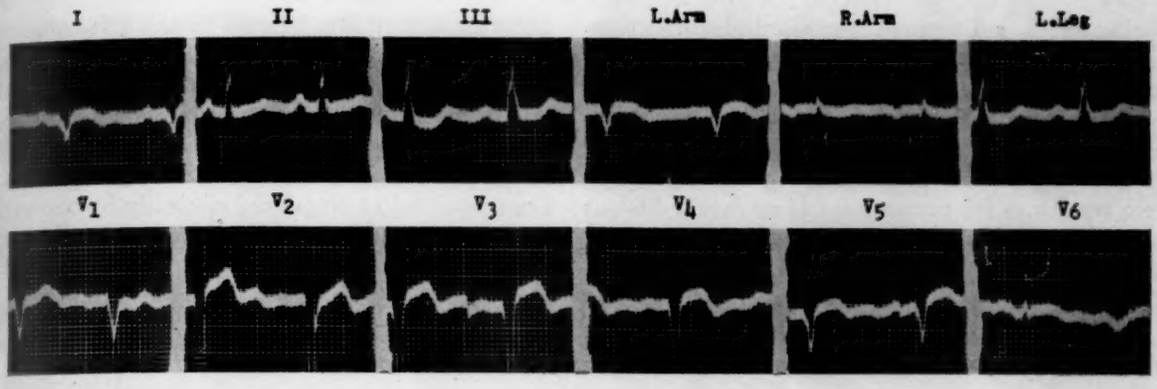

FIGURE 2. *Electrocardiogram in Case 1.*

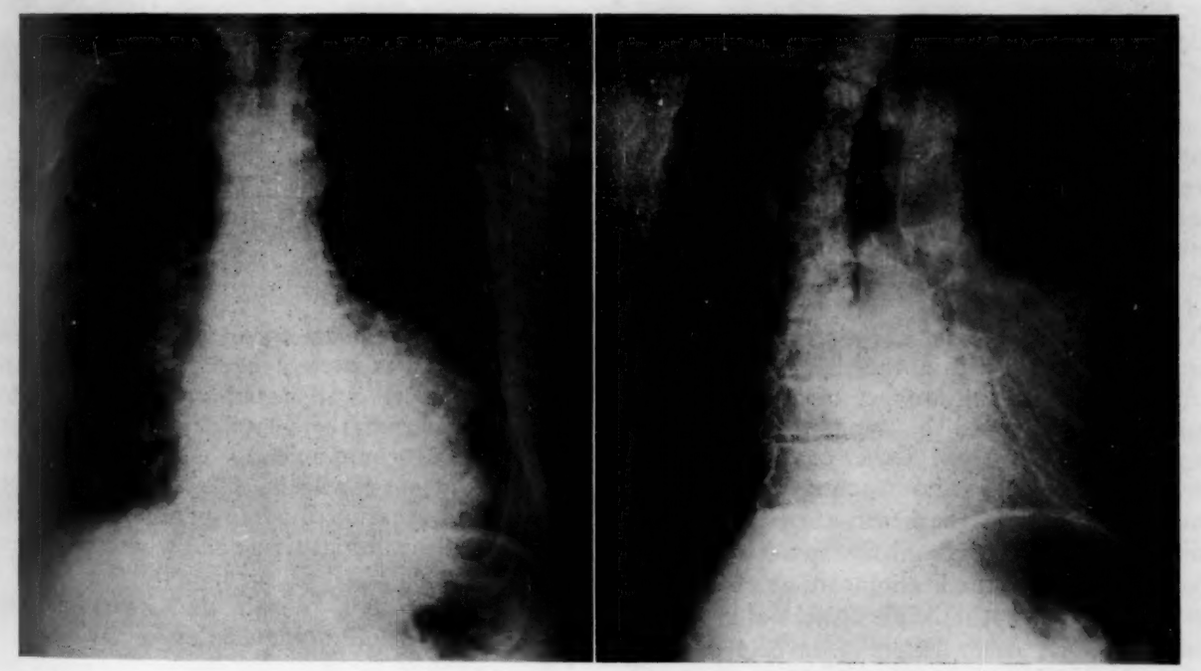

FIGURE 3. *Roentgenograms in Case 2.*

The photograph on the left shows the anteroposterior view, and that on the right the right oblique view.

Etiology

Pathogenesis

Although a small number of cardiac aneurysms are of rheumatic,[3, 9, 10] syphilitic,[1, 3] congenital,[3, 10-12] traumatic [9, 10] and mycotic[3, 9, 10] origin, the vast majority (at least 85 per cent)[13, 14] follow coronary occlusion with subsequent myocardial infarction. The infarct is followed by necrosis, which in turn leads to connective-tissue scarring. A variable number of subendocardial elastic fibers are involved. The damaged area behaves in an abnormal manner in that for a period intracardiac pressure during systole results in its expansion. If sufficient fibrous tissue replaces the muscular elements, a localized protrusion of the scar results. This protrusion, when present over a considerable length of time, becomes the chronic ventricular aneurysm. If the connective-tissue scar is not sufficiently strong to withstand the intracardiac pressures, rupture of the ventricle and death follow.

The factors that influence the integrity of the fibrous-tissue scar within the damaged area have been described as the number of attacks of myocardial infarction[15] and the amount of bed rest after the acute episode.[10, 14, 16] Other conditions, such as the presence of concomitant acute disease with increased demands on the heart, chronic pulmonary disease and lack of optimal therapy (oxygen), also affect the status of the healing cardiac musculature. The assumption that multiple attacks of myocardial infarction must occur before a cardiac aneurysm develops is unwarranted, since in 13 of 21 patients described by Brams and Gropper[16] there was a history of only one acute episode.

Other etiologic mechanisms should not be overlooked. Linck[11] reports a case due to congenital origin of the left coronary artery from the pulmonary artery; a few cases have been described[9] in which cardiac aneurysm followed gumma or infective endocarditis and abscess formation.

Site

Since most cardiac aneurysms follow myocardial infarction,[13, 14] the most frequent locations for ventricular aneurysms are the areas supplied by the anterior descending branch of the left coronary artery — namely, the apex, the anterior wall of the left ventricle and the anterior half of the interventricular septum. Aneurysm of the posterior wall is rare[3, 10] despite the frequency of posterior myocardial infarction, and to our knowledge has only been reported as diagnosed clinically by one author.[17] Although aneurysm of the interventricular septum may cause a Bernheim syndrome[9] and lead to its discovery by apparent right ventricular enlargement, in most cases this condition cannot be diagnosed during life.

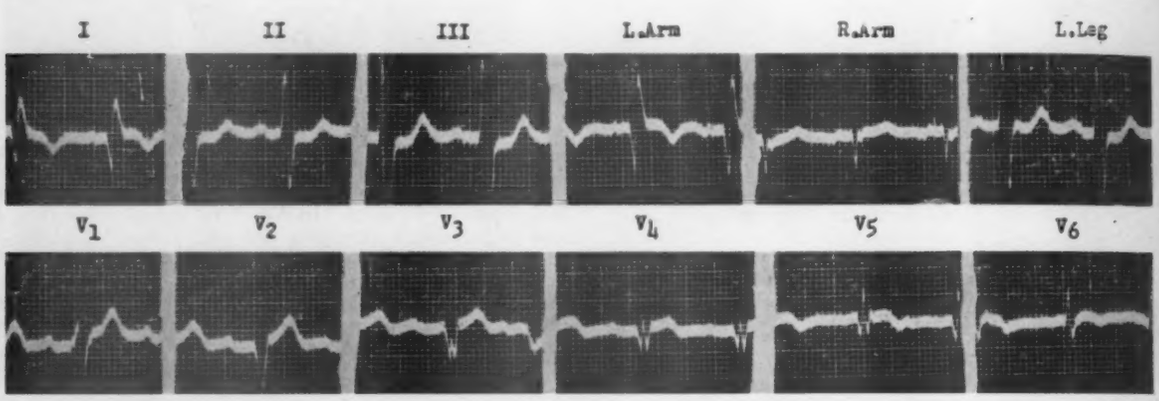

Figure 4. *Electrocardiogram in Case 2.*

Pathology

The shape of the aneurysm is variable. The most common type is merely a simple outpouching of the heart-muscle wall not sharply delineated from the remainder of the ventricle; occasionally, it is saccular and communicates with the ventricular cavity by means of a neck. The wall of the aneurysm is thin and occasionally transparent, and composed of replacement fibrous tissue and whatever muscular elements remain. It is covered by the firmly adherent pericardium. Within the aneurysm, thrombosis and eventually organization of the clot occur. Calcification of the wall, the clot or the pericardium occurs and may suggest the diagnosis roentgenologically. This calcification occurred in 30 per cent of 20 cases of ventricular aneurysm reported by Foord.[18] It should be noted that calcification of the pericardium may occur as an independent entity, and its presence is not a specific radiographic finding of cardiac aneurysm.

Cardiac aneurysms have been described as varying from the size of a small prune,[19] or a large duck's egg,[20-22] to an area equal to or greater than the heart itself.[20, 22] Sternberg[13] includes small, clot-containing cavities wholly within the cardiac wall as aneurysms, and states that thus many cardiac aneurysms are present that do not distort the cardiac contour. The average measurements of the cardiac aneurysm as observed in 21 cases at autopsy were 2 to 4 cm. in diameter and 1.2 to 3 cm. in depth.[2, 16] In the living patient, however, the apparent size of the aneurysm is greater, owing to the increased intracardiac pressure during systole. The aneurysm may be noted over a period to increase in size. Cardiac aneurysms are not infrequently multiple, and in the series of 21 cases described by Brams and Gropper[16] in which the aneurysm was found at autopsy, 6 had two or more such aneurysms.

Incidence

Aneurysm of the heart is stated by Parkinson, Bedford and Thomson[3] to occur in 9 per cent of patients suffering myocardial infarction. At the Massachusetts General Hospital in a series of autopsy cases examined between 1926 and 1945, Wang, Bland and White[24] found 52 large cardiac aneurysms in 556 patients with myocardial infarction, or an incidence of 10 per cent. An incidence of 10 per cent is also reported by Foord[18] in 107 cases of old myocardial infarction. It is interesting to observe that although these three papers are based on series in three widely separated geographical areas (England, Massachusetts and California) the relative percentage is the same. Others have found the incidence even higher.[25] Libman[26] points out that cardiac aneurysm occurs fifteen times as frequently as Hodgkin's disease. With the increased diagnosis of myocardial infarction,[24] it is evident that cardiac aneurysm should be recognized oftener during life.

The development of the aneurysm closely follows the occurrence of myocardial infarction, many appearing within a week to several months after the acute episode.[15, 17] It is obvious, therefore, that the age incidence for cardiac aneurysm parallels that of myocardial infarction.

Since the incidence of myocardial infarction is greater in men than in women, it is likewise not surprising to note Crawford's[9] statement that in a summary of the literature, 66 per cent of patients with cardiac aneurysms were males. In later papers, the incidence in males appears higher. Parkinson et al.[3] (1938) report 14 out of 15, Brams and Gropper[16] (1940) 20 out of 21, and Crawford[9] (1943) 11 out of 13.

Clinical Features

Symptoms

Practically all the symptoms in patients with cardiac aneurysms can be attributed to the underlying cardiac lesion. The aneurysm per se is asymptomatic except for occasional development of pain in the region of the apex.[20] The anginal syndrome or symptoms of left ventricular failure that may appear are not produced by the aneurysm but are related to the coronary artery or myocardial disease. Patients who have had so-called silent myocardial infarcts may develop cardiac aneurysms without any symptoms whatsoever.

Physical Signs

Some signs are described that make one suspect the existence of this lesion. On inspection, a pulsation that is plainly distinguishable from that of the apical beat is seen. This is forceful and heaving and is located just lateral to the left sternal border. With palpation, one may confirm the forcefulness and heaving character of the pulsation. Crawford[9] considers this sign of such importance that he states that its presence permits the diagnosis to be made by physical examination alone. The area of cardiac dullness is increased and sometimes is irregular in contour.

The heart sounds are usually diminished, but more characteristic is the "dull first heart sound with poor tone with little or no muscular quality."[27] This sign, together with abnormal pulsation, was described by Libman[26] in 1926 as being highly suggestive of the diagnosis of cardiac aneurysm. Others have concurred in the importance of these physical findings. Brams and Gropper[16] found pulsation present in 57 per cent of their 21 cases. Although not of diagnostic importance, other physical findings in cardiac aneurysm are a systolic murmur in the area of abnormal pulsation, which develops after a myocardial infarction, and a gallop rhythm. The mechanism of the gallop rhythm found in a case of ventricular aneurysm was studied in detail by LeRoy and Roberts,[28] who found that during systole the aneurysm bulged outward and by traction on the papillary muscle prevented the closure of the anterior leaflet of the mitral valve, resulting in auricular reflux of blood and producing a third heart sound.

The various arrhythmias that occur in severe myocardial disease are found in patients with cardiac aneurysm, and frequent extrasystoles, auricular fibrillation, auricular flutter and paroxysmal ventricular tachycardia have been described.[3]

A noteworthy feature of the clinical picture of cardiac aneurysm is the normal or low blood pressure. In a series of 15 cases,[3] no evidence of previous or present hypertension was found. In Crawford's[9] series of 13 cases, only 1 patient showed elevated

blood pressure. The blood pressure in Hartley's[10] 2 cases was reported as 110 systolic, 90 diastolic, and 150 systolic, 90 diastolic. Penner's[6] patient had a blood pressure of 140 systolic, 90 diastolic. Consideration of this important feature of blood pressure within the normal range led Parkinson, Bedford and Thomson[3] to raise the possibility that previous hypertension when associated with ventricular hypertrophy may exert a protective effect in preventing the development of a cardiac aneurysm. The thickened muscular wall of the ventricle is less likely to be involved in its entire thickness after coronary thrombosis, whereas the wall of a heart that has not undergone hypertrophy due to hypertension may be more easily involved in greater proportion, leading to the development of a cardiac aneurysm.

It must be noted, however, that in 1 of the 3 cases reviewed by Eliaser and Konigsberg[29] the patient had hypertension, as did 50 per cent of those in the series of Brams and Gropper.[16] The latter authors question the ability of the hypertrophied myocardium, which they consider abnormal muscle, to protect against the formation of cardiac aneurysms.

Electrocardiogram

There is no unanimity of opinion about the electrocardiographic pattern in ventricular aneurysm. The earliest papers, summarized by Eliaser and Konigsberg[29] in 1939, showed that 23.5 per cent of the tracings revealed a downward direction of the major deflection in Lead 1, with inversion of the T wave, whereas the ventricular complex was upright in Lead 3. On the other hand, in Crawford's[9] analysis of 13 cases, none of the electrocardiograms showed the changes described by the above authors. In 35.3 per cent of the cases reported to 1939,[29] a left-axis deviation was present, with major deflections directed downward in Lead 2 and Lead 3 with or without low amplitude of the ventricular complex in Lead 1. Some of the remainder showed left-bundle-branch block or equivocal records.

Nordenfelt,[30] in his electrocardiographic study of 10 cases, showed that when the aneurysm involved the anterior wall the following pattern often persisted: relatively low R or Q wave with negative T wave in Lead 1; deep S wave with upright T wave in Lead 2; deep S wave with upright T wave in Lead 3; and absent or low R wave and deep S wave in Lead 4. In all leads, the ST segment was elevated.

Sigler and Schneider[31] observed that the electrocardiogram is of no specific diagnostic value but that apical aneurysms seem to be associated with the pattern described above. Gross and Schwedel[32] have pointed out that there may be a progressive deviation of the electric axis to the right. Goldberger[33] mentions the pattern of low R wave in Lead 1 and deep S waves in Leads 2 and 3 as occurring occasionally in cases of ventricular aneurysm. In the most recent paper that we have seen in the literature on the electrocardiographic pattern of ventricular aneurysm, Goldberger and Schwartz[34] emphasize the value of the augmented unipolar right-arm lead. In 15 cases of ventricular aneurysm in which the standard leads were variable or tended to show the pattern of low R wave in Lead 1 and deep S waves in Leads 2 and 3, the right-arm lead revealed an upward deflection of the QRS complex, regardless of the site of the infarction or rotation of the heart. They regard this upward deflection of the QRS complex in the right-arm lead as so important that the diagnosis of ventricular aneurysm should not be made in its absence. One of our patients showed this finding (Fig. 2), whereas in Case 2 the pattern was atypical (Fig. 4).

It is apparent that there is no electrocardiographic pattern that is definitely characteristic of ventricular aneurysm. A low R wave in Lead 1, however, with deep S waves in Leads 2 and 3, is suggestive and, if associated with elevated ST segments in all leads, can be considered helpful. Persistence of this pattern for a considerable period is also helpful since regression of the pattern to normal often occurs after uncomplicated infarction. The presence of right-axis deviation with a heart obviously enlarged to the left is rare but may occur in patients with ventricular aneurysm. This right-axis deviation occurred in 27.3 per cent of the cases reported by Eliaser and Konigsberg.[29]

The variation in the electrocardiographic pattern found in ventricular aneurysm must be due to many other factors besides the presence of the ventricular aneurysm. It is obvious that progression of the underlying heart disease and recurrent myocardial infarcts influence the electrocardiogram. Other changes may be due to rotation of the heart, or to alterations in the thrombus within the aneurysm.[5]

X-ray Observations

The localized bulging of the left ventricular wall just above the apex is the most characteristic radiographic appearance of cardiac aneurysms. The x-ray diagnosis of the aneurysm in this site is comparatively easy. In the anteroposterior view, the bulge is most commonly seen just above the apex, and by means of fluoroscopy or lateral and oblique films, the portion of the ventricle involved is identified. In the oblique view, the cardiac silhouette shows an abrupt shelving of the anterior wall.[9] Sometimes, pulsation can be seen in the aneurysmal area, but most investigators agree that it is not a necessary criterion for the diagnosis.[17] When this paradoxical pulsation occurs in the bulge, it is almost pathognomonic. The bulge may become adherent to the pericardium, and, during systole, there may be expansion of the aneurysm with sub-

sequent involvement of the pleura or diaphragm. This systolic expansion is one of the bases for the diagnosis by roentgenkymography. Absent pulsation in this area is the other.

Secondary x-ray findings may be very valuable in the diagnosis. An intraventricular thrombus may cast a shadow of increased density; calcification within the thrombus or wall of the sac may likewise be noted. In this situation the clot is helpful in the x-ray diagnosis but by interference with the transmission of pulsation another important sign is obscured. Schwedel[17] describes an incisura between the bulge and the remainder of the left ventricular contour just above the diaphragm in the anteroposterior view.

Massive aneurysms involving the entire left ventricular wall are commonly overlooked, since the x-ray appearance is then merely one of an enlarged left ventricle.

Even though the most common site for cardiac aneurysm is the apex, this location does not lend itself to easy recognition by routine x-ray study. Surrounding structures, especially the diaphragm, obscure this area. Special technic, including examination under different phases of respiration and the use of effervescent substances to inflate the stomach, may be attempted to reveal the apical aneurysm protruding into the gas bubble.

Posterior-wall aneurysms, which are less common, have been demonstrated by Schwedel[17] by means of fluoroscopy and repeated radiographic examinations that showed progressive increase in size of the localized bulge. Occasionally, the barium-filled esophagus is displaced by the aneurysm of the posterior wall in the left oblique view.[9]

The aneurysm of the interventricular septum has never been diagnosed clinically to our knowledge. The presence of calcification in the septum, however, may lead to its recognition.

Angiocardiography may be of great help in the diagnosis since this method portrays the cardiac chambers and more clearly elucidates deformities of the cardiac contours. It is obvious that a clot may interfere with the deposition of the radiopaque substance within the cardiac chamber, and hence the continuity or communication of the deformity of the cardiac shadow with the intraventricular cavity may not be demonstrated and a ventricular aneurysm may be missed.

Differential Diagnosis

Only a few conditions are encountered commonly enough to be considered in the differential diagnosis of cardiac aneurysm. Primary tumors of the heart and pericardium are exceedingly rare.[35] Metastatic tumors may be considered when an unusual cardiac bulge is seen in a heart that is not enlarged, and when the bulge pulsates synchronously with the remainder of the heart. Occasionally, the diagnosis may be suspected in patients with known cancer, or in cases of unexplained heart block.[36]

Localized pericardial fluid may be differentiated by the history of pericarditis and the nature of the pulsation.

Aneurysms of the descending aorta can usually be distinguished by fluoroscopy and possibly by angiocardiography. A diastolic murmur and a positive serologic test for syphilis will aid in the recognition of an aneurysm of the sinus of Valsalva when it projects to the left.

Diseases associated with pulmonary hypertension may enlarge the conus arteriosus so that it simulates cardiac aneurysm. Carefully performed fluoroscopy will demonstrate that the area involved consists of the entire pulmonary conus rather than a localized ventricular bulge, and the type of cardiac murmur (in cases of mitral stenosis), the presence of congenital heart disease or signs of pulmonary disease aid in this differentiation.

Extracardiac lesions that produce apparent deformities of the cardiac silhouette and may be confused with a cardiac aneurysm are tumors of the mediastinum or lung. Of these, dermoids occur at a younger age and are usually asymptomatic except for pressure symptoms, and there is no antecedent history of myocardial infarction. Sometimes the tumors contain teeth or other bony structures, which are seen on x-ray examination. Teratomas of the mediastinum may distort the cardiac configuration[37] but may be associated with teratomas elsewhere, as in the ovary or testis.

Other benign or malignant intrathoracic tumors are less common but may be confusing when in close proximity to the ventricular shadow.[36] With the development of the technic of visualization of the cardiac chambers and related structures by the injection of 70 per cent diodrast solution most of these extracardiac lesions can be delineated.

A diverticulum of the pericardium projects to the right in contrast to the usual left-sided cardiac aneurysm. Hydatid cyst of the pericardium can be differentiated by appropriate skin and serologic tests. The para-apical fat triangle is easily differentiated by x-ray examination.

Clinical Course

The presence of a cardiac aneurysm does not in itself affect the clinical course. The underlying cardiac disease, rather than the existence of the aneurysm, determines the development of anginal pains, signs or symptoms of congestive heart failure, arrhythmias or even death. Recurrent acute episodes should not be attributed to the cardiac aneurysm but to the progressive coronary-artery and myocardial disease. Fisher[38] has recently reported a case of cardiac aneurysm with rupture. In 1944 Beck[39] described a case of ventricular aneurysm in which he grafted a segment of fascia lata over the aneurysm in the hope of preventing

its rupture. This patient died a few weeks later of a complicating pneumonia. This direction of surgical effort although brilliant seems unwarranted since Levine[35] has stated that rupture of the chronic ventricular aneurysm rarely if ever occurs. In the two largest series of cases that we have encountered,[16, 17] no case of rupture of the cardiac aneurysm took place.

The prognosis of ventricular aneurysm, therefore, depends on the pre-existing coronary-artery disease, and since this may be static or actually improved by the development of collateral circulation there are many reports of longevity[3-8] in the literature. In fact, some of these patients have done and are doing manual labor, and many have carried on the normal activities of daily living without untoward incident. The presence of more than one cardiac aneurysm does not seem to alter the prognosis.[16]

In some aneurysms thrombosis and fibrosis do not occur, and because of progressive enlargement the wall of the sac becomes thin, its only support being that of the adherent pericardium. It is in this rare type that rupture may take place. Another of the relatively few complications of the aneurysm itself is the development of embolic phenomena. A small portion of the intra-aneurysmal clot may detach itself and result in hemiplegia, gangrene of the feet, or infarcts of the viscera, kidneys or skin.[3, 10, 20]

Discussion

If one accepts the statement of Parkinson, Bedford and Thomson[3] that 1 out of every 11 patients with myocardial infarction will develop cardiac aneurysm and the autopsy figures of the Massachusetts General Hospital[24] showing a 10 per cent incidence of cardiac aneurysm in patients after myocardial infarction, it appears that many cases are being missed clinically. Sigler and Schneider[31] state that only 0.5 per cent have been diagnosed during life and support our impression that the diagnosis should be made more frequently. It might be well, therefore, to review the important diagnostic features of cardiac aneurysm.

A history of previous infarction can usually be elicited although silent myocardial infarction must be kept in mind.

The presence of abnormal pulsations within the area of cardiac dullness but separate and distinct from the apical impulse may be seen.

A poor, dull first sound despite the increased pulsations may be present.

A localized bulge sometimes accompanied by increased density, calcification, pericardial adhesion or incisura (Schwedel) may be demonstrated.

There are also a number of findings that are not in themselves as definitive as those listed above, but their presence should lead to the awareness of the possibility that a ventricular aneurysm exists: an enlarged heart with distant heart sounds; an enlarged heart with the physical finding of normal blood pressure[3]; an enlarged heart with the electrocardiographic finding of right-axis deviation or the finding of an upward deflection of the QRS complexes in the right-arm lead[34]; and the late occurrence of cerebral or other embolism in a patient who has had a myocardial infarction.[3]

In view of the recent emphasis on early ambulation after myocardial infarction, a warning note about the pathogenesis of cardiac aneurysm must be sounded. It has frequently been pointed out[10, 14, 16, 40] that many patients who have developed ventricular aneurysms have received inadequate bed rest after the acute episode of infarction. Zimdahl and Busuego[40] considered it significant in the development of the aneurysm in one of their patients that he was sent back and forth to a diagnostic laboratory for three days after his attack. Some patients may have had the silent type of myocardial infarction, and no bed rest at all was prescribed. During the period of myomalacia every precaution must be taken to support the weakened myocardium, and undoubtedly bed rest reduces the work of the heart and allows a firmer scar to develop.

It will be interesting to note the effect on the incidence of rupture of ventricular aneurysm of the introduction in 1945[41] of anticoagulant therapy for myocardial infarction. Reduction of clot formation within the aneurysm theoretically may result in a thin-walled sac that does not have the support of a firm, lamellated clot. The x-ray diagnosis may be more difficult because of the lack of increased density and calcification in the bulge. This type, having only the pericardium as its support, tends to increase its size and is more likely to rupture. On the other hand, the late embolic manifestations mentioned above may be prevented.

Summary

Two cases of ventricular aneurysm diagnosed during life are reported. The patients are not incapacitated by their cardiac aneurysms, and their cardiac symptoms are referable to the underlying cardiac disease.

The increased incidence, physical and x-ray findings, and clinical course of cardiac aneurysm are reviewed. Certain criteria for the ante-mortem diagnosis, as well as the brighter outlook regarding prognosis and longevity, are stressed.

The effect on cardiac aneurysms of two recently introduced regimens in the therapy of myocardial infarction — early ambulation and anticoagulant therapy — are briefly discussed.

References

1. Vilk, N. L., and Rabinovich, M. P. Aneurysm of heart due to syphilis. *Russk. klin.* **13**:280-288, 1930.
2. Ushtchantzeff, S. A. Diagnosis in vivo of aneurysm of cardiac ventricles. *Klin. med.* **9**:534-538, 1931.
3. Parkinson, J., Bedford, D. E., and Thomson, W. A. R. Cardiac aneurysm. *Quart. J. Med.* **7**:455-478, 1938.
4. Dressler, W., and Pfeiffer, R. Cardiac aneurysm: report of ten cases. *Ann. Int. Med.* **14**:100-121, 1940.

5. Young, D., and Schwedel, J. B. Longevity in ventricular aneurysm: report of case followed over ten year period. *Ann. Int. Med.* **21**: 141-149, 1944.
6. Penner, S. L., and Peters, M. Longevity with ventricular aneurysm: report of case with survival period of fifteen years. *New Eng. J. Med.* **234**:523-526, 1946.
7. Berk, L. H. Cited by Young and Schwedel.[5]
8. Robertson, G. H. Cardiac aneurysm, with account of case followed over unusually long period. *New Zealand M. J.* **45**:527-534, 1946.
9. Crawford, J. H. Aneurysm of heart. *Arch. Int. Med.* **71**:502-515, 1943.
10. Hartley, G. S. Cardiac aneurysm. *West Virginia M. J.* **36**:64-68, 1940.
11. Linck, K. Aneurysmatische Erweiterung der linken Herzkammer infolge Ursprungs der linken Kranzschlagader aus der Pulmonalis bei einem 8 Monate alten Mädchen. *Virchows Arch. f. path. Anat.* **297**:113-118, 1936.
12. Posselt, A. Über klinische Diagnose von Aneurysmen des membranösen Septums der Vorhofscheidewand bei angeborenen Herzfehlern. *Ztschr. f. klin. Med.* **121**:50-77, 1932.
13. Sternberg, M. *Das chronische partielle Herzaneurysma. Anatomie, Klinik, Diagnose.* 76 pp. Leipzig: Franz Deuticke, 1914.
14. Rowland, D. Cardiac aneurysm: report of case with correlation of clinical, radiological and electrocardiographic findings. *Ann. Int. Med.* **19**:349-356, 1943.
15. Shookoff, C., and Douglas, A. H. Case of acute coronary occlusion with roentgenographic evidence of early development of aneurysm of left ventricle. *Am. Heart J.* **7**:95-100, 1931.
16. Brams, W. A., and Gropper, A. Cardiac aneurysm: evaluation of its clinical features. *Illinois M. J.* **78**:246-252, 1940.
17. Schwedel, J. B. Ventricular aneurysm. In *Clinical Roentgenology of the Heart.* 380 pp. New York: Paul B. Hoeber, Inc., 1946. Pp. 87-99.
18. Foord, A. G. Embolism and thrombosis in coronary heart disease. *J. A. M. A.* **138**:1009-1012, 1948.
19. Längle, I. Zum Röntgenbild des Herzwandaneurysmas. *Wien. klin. Wchnschr.* **59**:685-688, 1947.
20. Lutembacher, R. Anévrismes du ventricule gauche. *Arch. d. mal. du coeur* **13**:49-58, 1920.
21. Norris, G. W., and Landis, H. R. M. *Diseases of the Chest and the Principles of Physical Diagnosis.* Sixth edition. 1019 pp. Philadelphia: W. B. Saunders Co., 1938. P. 812.
22. Moukhtar, A., and Sédad. Large communication interauriculaire avec anévrisme de la pointe du coeur gauche. *Bull. et mém. Soc. méd. d. hôp. de Paris* **50**:402-404, 1926.
23. Legg, J. W. *Some Account of Cardiac Aneurysms.* 75 pp. London: J. & A. Churchill, 1884.
24. Wang, C. H., Bland, E. F., and White, P. D. Note on coronary occlusion and myocardial infarction found post mortem at Massachusetts General Hospital during twenty year period from 1926 to 1945 inclusive. *Ann. Int. Med.* **29**:601-606, 1948.
25. Appelbaum, E., and Nicolson, G. Occlusive diseases of coronary arteries: analysis of pathological anatomy in 168 cases, with electrocardiographic correlation in 36 of these. *Am. Heart J.* **10**:662 680, 1935.
26. Libman, E. Methods of physical examination, with special reference to painful disease of thorax and abdomen. *Proc. Inter-State Post-Grad. M. A., North America* (1926), pp. 60-66, 1927.
27. Ball, D. Aneurysm of heart: clinical recognition of aneurysm of left ventricle. *Am. Heart J.* **16**:203-218, 1938.
28. LeRoy, G. V., and Roberts, R. C. Systolic gallop rhythm as sign of aneurysm of left ventricle: report of case. *Am. Heart J.* **21**: 115-119, 1941.
29. Eliaser, M., Jr., and Konigsberg, J. Electrocardiographic findings in cases of ventricular aneurysm. *Arch. Int. Med.* **64**:493-504, 1939.
30. Nordenfelt, A. Electrocardiogram in chronic aneurysm of heart. *Acta med. Scandinav.* **102**:101-123, 1939.
31. Sigler, L. H., and Schneider, J. J. Diagnosis of cardiac aneurysm with report of two cases. *Ann. Int. Med.* **8**:1033-1046, 1935.
32. Gross, H., and Schwedel, J. B. Clinical course in ventricular aneurysm. *New York State J. Med.* **41**:488-491, 1941.
33. Goldberger, E. *Unipolar Lead Electrocardiography: Including standard leads, unipolar extremity leads and multiple unipolar precordial leads.* 182 pp. Philadelphia: Lea & Febiger, 1947. P. 134.
34. Goldberger, E., and Schwartz, S. P. Electrocardiographic patterns of ventricular aneurysm. *Am. J. Med.* **4**:243-247, 1948.
35. Levine, S. A. *Clinical Heart Disease.* Third edition. 462 pp. Philadelphia: W. B. Saunders Co., 1945. P. 113.
36. Alquier. Opacités arrondies intra-thoraciques d'interprétation difficile. *Bull. et mém. Soc. d'electro-radiol. méd. de France* **27**: 670-674, 1939.
37. Horowitz, I. Teratoma of mediastinum: case report. *Connecticut State M. J.* **11**:978-982, 1947.
38. Fisher, R. L. Cardiac aneurysm with rupture. *Am. Heart J.* **30**: 133-140, 1945.
39. Beck, C. S. Operation for aneurysm of heart. *Ann. Surg.* **120**:34-40, 1944.
40. Zimdahl, W. T., and Busuego, S. Ventricular aneurysm: report of two cases. *Am. Practitioner* **3**:185-190, 1948.
41. Wright, I. S. Experiences with dicumarol in treatment of coronary thrombosis. *Proc. Am. Federation Clin. Research* **2**:101, 1945.

OSTEITIS PUBIS*

M. Abrams, M.D.,* I. Sedlezky, M.D.,† and David B. Stearns, M.D.‡

BOSTON

THE number of reported cases of osteitis pubis following suprapubic or retropubic prostatectomy[1-11] suggests that it is a rare complication. Since this is not in accord with our own experience we herewith present 5 cases with observations relating to diagnosis and treatment. Two of them followed retropubic prostatectomy, and 2 followed suprapubic prostatectomy; the fifth case followed an abdominoperineal resection for carcinoma of the rectum.

Case Reports

Case 1. J. W., a 61-year-old man, was admitted to the hospital with the chief complaint of frequency of urination during the day and night and hesitancy and diminution in the force of the urinary stream. An examination of the urine revealed 15 to 20 white cells and 3 to 5 red cells per high-power field. Urine culture grew out many colonies of hemolytic *Staphylococcus aureus*. The findings of the lower urinary tract were consistent with an obstructing prostate. Three days later a retropubic prostatectomy was done. The postoperative course was uneventful.

Thirty-eight days after the operation the patient first began to notice pain over the symphysis pubis. The pain gradually became worse, and 12 days thereafter he was readmitted to the hospital. Coughing, walking or motion of the legs in any direction increased the severity of the pain. Except for marked tenderness over the symphysis pubis, physical examination was entirely negative.

The white-cell count was 15,000; the blood acid and alkaline phosphatase, as well as the phosphorus, were normal. Urine culture showed a few colonies of *Pseudomonas aeruginosa* and *Staph. albus*. A roentgenogram taken the day after admission showed some irregularity and erosion of the upper edges of the inner margins of the pubic bones. Successive films demonstrated progressive destruction of the medial margins of the pubic bones. Healing was demonstrated by the laying down of dense bone at the articular margins of the pubis.

Streptomycin, penicillin, sulfadiazine and sulfamerazine failed to alter the clinical course of the disease. Diathermy and local heat were ineffective. Opiates were necessary to control the pain and discomfort. At the end of 3 weeks, an orthopedic belt, which had only aggravated the symptoms in the acute phase of the disease, now gave definite relief. Improvement occurred slowly. The patient was free of all pain 9 weeks after the onset of symptoms.

Case 2. M. H., a 74-year-old man, was admitted to the hospital in acute urinary retention. For 1 year prior to admission he had complained of nocturia three to five times and of difficulty in starting the urinary stream. The prostate on rectal examination was very large. Examination of the urine revealed 3 to 5 white cells per high-power field. Culture of

*Assistant in genitourinary surgery, Harvard Medical School; resident in urology, Beth Israel Hospital.

†Resident in radiology, Beth Israel Hospital.

‡Assistant professor of urology, Boston University School of Medicine; visiting urologist, Massachusetts Memorial Hospitals; associate visiting urologist, Beth Israel Hospital.

the urine grew out a few colonies of *Ps. aeruginosa*. Five days later a retropubic prostatectomy was done. The postoperative course was uneventful. A urine culture taken the day the catheter was removed grew out many colonies of *Aerobacter aerogenes* and *Ps. aeruginosa*.

Twenty-nine days after operation the patient began to complain of a constant dull pain over the symphysis pubis and along the inner aspects of both thighs. Coughing, walking or sitting aggravated the pain. There was definite localized tenderness over the symphysis pubis. On examination the white-cell count was 12,000; the acid and alkaline phosphatase levels were normal. A culture of the urine grew out *Ps. aeruginosa*. A roentgenogram of the pelvis taken 7 days after the onset of symptoms revealed slight erosion of the right os pubis. Another roentgenogram taken 1 month later demonstrated further destruction of the upper medial corner of the left os pubis. Penicillin, streptomycin and sulfadiazine had no effect on the clinical course of the disease. Large doses of vitamin B given intravenously in conjunction with a course of deep x-ray therapy proved ineffective. An orthopedic belt, which extended from above the crest of the ilium to below the symphysis pubis, allowed the patient to become ambulatory 2 weeks after the onset of symptoms. Six weeks later he was entirely free of pain.

CASE 3. F. W., a 66-year-old man, had a two-stage suprapubic prostatectomy for a benign prostatic hypertrophy. Numerous calculi were present within the prostate. After the second stage, the immediate postoperative course was complicated by the development of epididymitis. The elevated temperature returned to normal in 6 days, and no additional surgical procedure was necessary. Four months after operation the patient first began to complain of a dull aching pain in both groins. The pain was referred to the perineum and along the inner aspects of both thighs. Gradually these symptoms became worse, and 2 months thereafter the discomfort required hospitalization.

Physical examination revealed an elderly man in obvious pain. Coughing, sitting or any movement of the lower extremities increased the severity of the symptoms. There was definite tenderness over the symphysis pubis. On examination the urine contained 15 to 20 white cells and 5 to 10 red cells per high-power field. Culture of the urine showed many colonies of *Ps. aeruginosa*, as well as a moderate number of *Escherichia coli*. The blood calcium, acid phosphatase, alkaline phosphatase and phosphorus were normal. A roentgenogram of the pelvis demonstrated the wide symphysis pubis that is consistent with osteitis pubis. Films taken with the patient standing first on the left foot and then the right foot revealed the extreme mobility of the pubic bones at this time (Fig. 1*B* and *C*). Immobilization of the pubis with a tight orthopedic belt gave the patient some relief. Eight days later he was ambulatory with the aid of a cane. Twenty days later he was discharged, very much improved, but still unable to walk without the aid of the tight belt and cane. A roentgenogram taken 1 year later showed an irregularly widened symphysis pubis. The bony margins were dense, and the adjacent bone sclerotic. This represented a healed process (Fig. 1*D*).

CASE 4. A. M., a 71-year-old man, had a two-stage suprapubic prostatectomy for a benign hypertrophy of the prostate

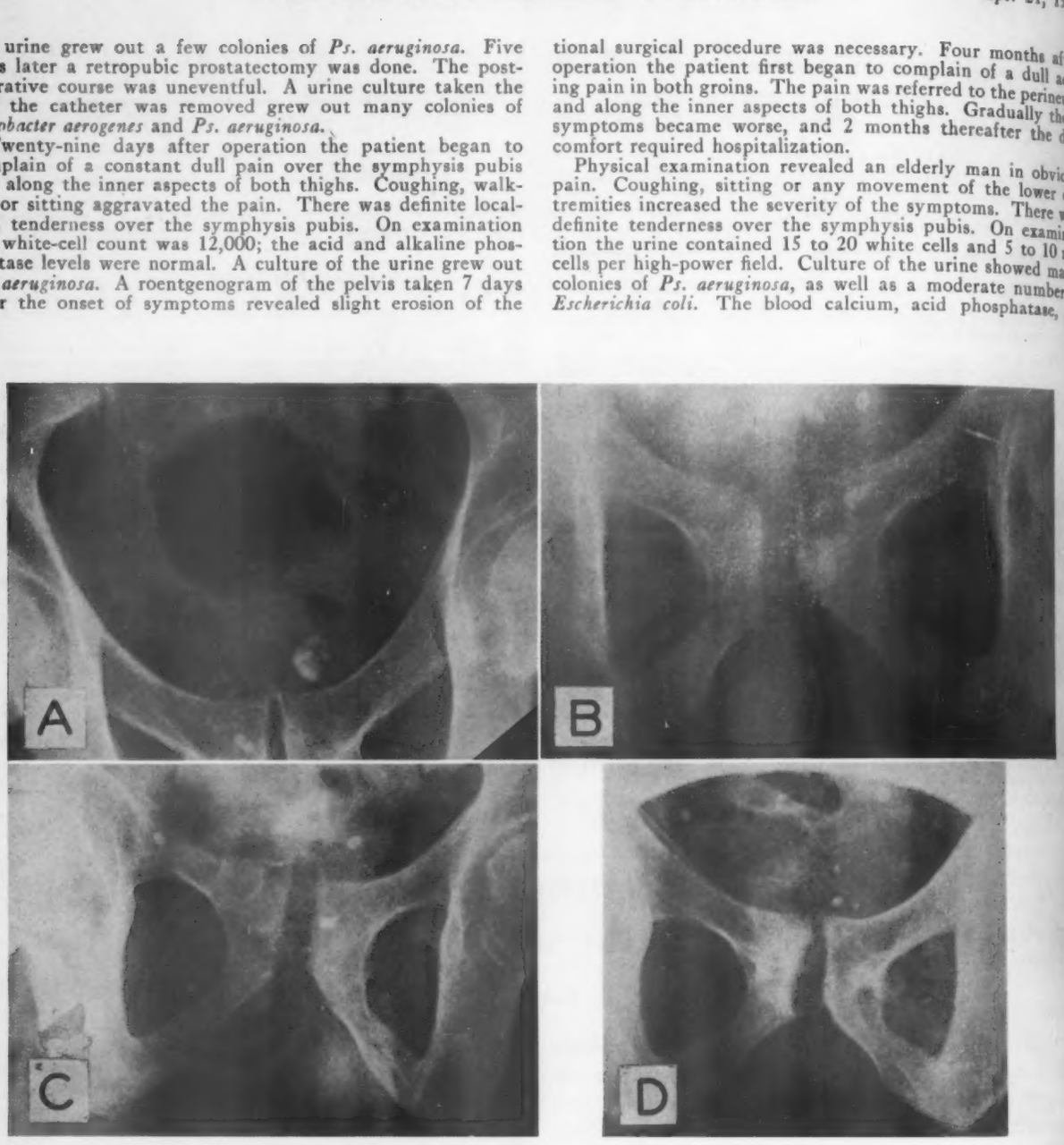

FIGURE 1. *Roentgenograms in Case 3.*

A = preoperative film, showing normal symphysis pubis (note prostatic calculi). B and C = films taken six months after suprapubic prostatectomy, with the patient standing first on the left foot and then on the right (note the wide symphysis and considerable mobility of the pubic bones). D = film taken eighteen months after operation, showing the symphysis pubis to be irregularly widened (the bony margins are dense, and the adjacent bone sclerotic; the process is apparently healed).

in another hospital. He was discharged 25 days after the second operation with a small, draining suprapubic sinus. Urinary control was excellent. Seventy-seven days after operation he was admitted for the first time to the Massachusetts Memorial Hospitals because of severe pain over the symphysis pubis and across the inner aspects of both thighs. Coughing, walking or motion of the legs in any direction aggravated the pain. These symptoms had begun 3 weeks earlier and had gradually become worse. There was tenderness on pressure over the symphysis pubis. A slight purulent discharge at the lower angle of the suprapubic wound was noted. The rest of the examination was entirely negative.

On admission, the urine contained many white cells and 2 or 3 red cells per high-power field. Culture of the urine grew out *Ps. aeruginosa* and *Esch. coli*. The white-cell count was 15,500. The acid and alkaline phosphatase determinations were normal. A roentgenogram of the pelvis showed a wide symphysis pubis with irregular erosion of the bone surfaces (Fig. 2). A diagnosis of osteitis pubis was made. Two days later a course of deep x-ray therapy was given. The patient received 200 r daily for 6 days over the pubis. Large doses of components of the vitamin B complex were also given. On the 4th day of therapy, definite improvement was noted. Four days later, the patient was able to move with only moderate discomfort. Seven days later he was discharged totally free from symptoms. The sinus at the lower end of the incision was healed. (No antibiotics or sulfonamides were given to this patient.)

FIGURE 2. *Roentgenogram Taken in Case 4 Seventy-Seven Days after a Suprapubic Prostatectomy.*
Note the unusually wide symphysis, with irregular erosion of the bony surfaces; the pubic bones show patchy rarefaction.

CASE 5.* E. S., a 50-year-old man, was admitted to the Massachusetts Memorial Hospitals for an abdominoperineal resection for an adenocarcinoma of the rectum. He had a moderately febrile postoperative course. Two months thereafter he was readmitted to the hospital because of constant pain over the symphysis pubis. Standing, sitting, coughing or walking increased the severity of the pain. On admission the temperature was 101°F. Examination of the urine showed 5 to 6 white cells per high-power field. Urine culture grew out many colonies of *Ps. aeruginosa* and hemolytic *Staph. aureus*. The white-cell count was 12,000. Physical examination revealed a functioning colostomy, a small draining sinus at the lower end of the abdomonal incision and tenderness to even slight palpation over the symphysis pubis. Cultures from the draining sinus grew out *Ps. aeruginosa*. A roentgenogram of the pelvis demonstrated beginning erosion of the medial surfaces of both pubic bones with widening of the symphysis.

Penicillin and sulfadiazine were started on admission. Four days later the temperature returned to normal. However, the pain over the symphysis pubis persisted for 3 weeks, when gradually it began to subside. Four weeks later the patient was free of all pain. A roentgenogram taken 7 months after the operation again demonstrated a wide symphysis pubis. Healing was clearly represented by the irregular, dense and sclerotic medial margins of the pubis.

*Permission to cite this case was obtained from Dr. C. Howe.

DISCUSSION

Although the etiology of this condition remains obscure, the symptoms, physical findings, laboratory data and course are all suggestive of an inflammatory process. Wheeler,[5] on the basis of his experimental studies, did not consider osteitis pubis as an inflammatory process. He attempted to reproduce this disease in the rabbit by introducing urine, both sterile and infected, under the periosteum of the pubis. This failed to produce any evidence of periostitis. The introduction of foreign bodies under the periosteum and even deliberate trauma to the space of Retzius failed to reproduce periostitis or osteitis. Wheeler therefore preferred to consider this syndrome as an example of acute bone atrophy of the Sudeck type. Sudeck's acute bone atrophy has been described[12] as a post-traumatic type of lesion that usually occurs in the neighborhood of multiarticular joints such as the wrist and foot and is regarded as a neurovascular disturbance. In addition to pain over the involved joint there is swelling, atrophy of the subcutaneous tissues and trophic changes in the skin. Roentgenologically, there is very marked decalcification of the bones.

We believe that osteitis pubis is of an inflammatory nature. The urine that escapes into the space of Retzius during and after operation slowly saturates and puddles in the retropubic soft tissues and sets up an inflammatory process that progresses so that the bone eventually becomes involved. At this point the clinical symptoms become evident. Although no bone biopsies were taken in any of the cases reported above, Muschat[7] reports a curettage biopsy of the symphysis pubis in a patient suffering from osteitis pubis. The specimen showed inflammation. Chemotherapy failed to alter the clinical course of the disease in any of our cases. Trauma to the symphysis pubis — by retractors, drains or needle puncture — may be a factor in the development of this clinical entity. The fact that osteitis pubis occurs so infrequently in women after extensive gynecologic operations suggests that trauma alone is not the sole cause.

The diagnosis of osteitis pubis offers no particular problem clinically. A history of a recent prostate operation and the development of localized pain over the symphysis should immediately suggest this condition. The pain, which is at first mild, soon becomes severe and radiates to the perineum and over the inner aspects of the thighs. Any motion

of the lower extremities increases the intensity of the pain. The pain is probably the result of muscle pull on the inflamed periosteum, in addition to increased intraosseous tension. In the 5 cases reported above, pain over the symphysis pubis appeared as early as twenty-nine days (Case 2), and as late as a hundred and twenty days after operation (Case 3). Some authors report these symptoms as early as fourteen days after the operation. Physical findings are usually entirely negative except for the localized tenderness over the symphysis pubis. A suprapubic sinus is occasionally found (Cases 4 and 5). During the early stages of the disease the patient usually has a mild fever. A white-cell count of 12,000 to 15,000 was present in all our cases. A moderate anemia was noted in Cases 4 and 5. The blood calcium, phosphorus, acid and alkaline phosphatase were normal. Examination of the urine revealed many white cells. Cultures of the urine grew out *Ps. aeruginosa*, *Esch. coli* and hemolytic *Staph. aureus*. *Ps. aeruginosa* was predominant and present in all cases.

Though this condition can be suspected on the basis of the clinical features, the final diagnosis rests on the roentgenologic findings. The technic of x-ray examination is important. The use of a fine-focus tube, a small cone and a Bucky diaphragm with the patient in the prone position are all essential factors in demonstrating the earliest bony changes. Stereoscopic films may be of help. The rectum should be free of gas and feces.

In general, roentgenographic changes have been observed two or three weeks after the onset of symptoms. However, in 1 case (Case 2) changes were noted as early as seven days. The earliest changes consist of blurring of the symphyseal contours of the pubis, with patchy osteoporosis of the contiguous bone. As the process continues bilateral, irregular and progressive destruction of the opposing articular surfaces of the symphysis pubis occurs. This is largely symmetrical, but one side may be more involved. No sequestra are produced or expected since the bone involved is predominantly spongy. It is a fact that necrotic, spongy bone is removed by resorption, and only compact bone by sequestration.[13] The progressive widening of the symphysis pubis is predominantly the result of loss of bone substance rather than just a separation of the pubic bones. The changes in the symphysis pubis are sufficient to permit considerable vertical mobility of the pubic bones. To show this, films were taken with the patient standing first on one foot and then on the other (Fig. 1*B* and *C*).

The healing period is variable, depending upon the extent of the lesion. Most authors agree that this period varies from two to six months. Roentgenologically, healing is signalled by the arrest in the progress of the bone destruction and the laying down of dense bone at the margins of the eroded symphysis pubis. Cases have been described in which the end result is ankylosis of the symphysis pubis.

The differential diagnosis included a simple prevesical-space infection without bone involvement, acute and chronic hematogenous osteomyelitis of the pubic bone, a metastatic lesion from the prostate and primary bone sarcoma.

A simple infection of the space of Retzius without bone involvement should offer no problem in the differential diagnosis. The clinical course is mild, and roentgenologic changes are absent. An acute hematogenous pyogenic osteomyelitis will give a more severe, more acute systemic reaction as well as more pronounced local changes. A specific chronic infection such as tuberculosis can be less easily ruled out purely on the basis of the initial roentgenographic changes. Tuberculosis of the symphysis pubis is extremely rare. The initial destructive phase may be difficult to distinguish from a metastatic lesion from a prostatic carcinoma. The characteristic restricted localization of bone resorption to the pubis, the history of a recent prostatic operation, the low-grade febrile course and the prominence of osteolysis with little or no osteoblastic features are against a metastatic lesion from the prostate. The acid and alkaline phosphatase was normal in the 5 cases of osteitis pubis reported above. The lack of periosteal reaction and the absence of spiculation or tumor mass are all against a diagnosis of primary bone sarcoma.

There is no specific treatment for this clinical entity. In the acute phase the intense suprapubic pain forces the patient to complete bed rest. Opiates and sedatives are necessary to keep the patient comfortable. In our cases, the use of penicillin, streptomycin and sulfadiazine did not in any way alter the course of the disease. Diathermy and local heat over the symphysis had little effect. The injection of 1 per cent novocain into the painful spastic muscles of the upper thigh occasionally gave temporary relief. In 1 case the use of deep x-ray therapy appeared to be beneficial. In 2 other cases in which it was tried it was of no benefit. Large doses of components of the vitamin B complex were also ineffective. After the subsidence of the acute process, which lasted between eighteen and twenty-one days, an orthopedic belt, extending from above the crest of the ilium to below the symphysis pubis, immobilized the symphysis pubis and proved beneficial. This belt, with the aid of a cane, allowed early motion. Relief of symptoms occurred slowly.*

Summary

Five cases of osteitis pubis are reported. Two of them followed retropubic prostatectomy; 2 followed suprapubic prostatectomy; and the fifth an abdominoperineal resection for carcinoma of the rectum. We do not know the specific etiology of

*Since this paper was submitted for publication, 4 additional cases of osteitis pubis have been reported, 2 after retropubic surgery and 2 after transurethral resection.[14]

osteitis pubis but consider it to be inflammatory. Trauma to the symphysis pubis, by retractors, drains or needle puncture, may be a factor in the development of this clinical entity. The fact that osteitis pubis occurs so infrequently in women after extensive gynecologic operations suggests that trauma alone is not the sole cause.

The diagnosis of osteitis pubis offers no particular problem. A history of a recent prostatic operation and the development of localized pain over the symphysis pubis should immediately suggest this entity. The roentgenologic findings are typical and definitely establish the diagnosis. The medial articular aspects of the pubic bones are predominantly involved. First there is merely blurring of the bony contours associated with osteoporosis of the adjacent bone. Then, there is slow, progressive erosion of the symphyseal aspects of the pubic bones. Healing is shown by arrest in the progress of the bone destruction and the laying down of dense sclerotic bone at the margins of the widened symphysis pubis. Urine cultures in the 5 cases reported grew out *Pseudomonas aeruginosa*. The significance of this finding is not established.

There is no specific treatment of osteitis pubis. Although deep x-ray therapy and large doses of components of the vitamin B complex appeared to help 1 patient, they proved of no help in 2 other cases. Penicillin, streptomycin, sulfadiazine and sulfathiazole were ineffective in controlling any of the symptoms. The disease, though distressing and of long duration, is self limited and does not require surgical intervention.

References

1. Beer, E. Periostitis of symphysis and descending rami of pubes following suprapubic operations. *Internat. J. Med. & Surg.* **37**:224, 1924.
2. *Idem.* Periostitis and ostitis of symphysis and rami of pubis following suprapubic cystotomies. *J. Urol.* **20**:233-236, 1928.
3. Kretschmer, H. L., and Sights, W. P. Periostitis and ostitis pubis following suprapubic prostatectomy: report of case with recovery. *J. Urol.* **23**:573-580, 1930.
4. Goldstein, A. E., and Ferber, W. L. F. Periostitis and osteitis pubis complicating suprapubic cystotomy: report of 6 cases. *J. Mt. Sinai Hosp.* **4**:1052-1058, 1938.
5. Wheeler, W. K. Osteitis pubis following suprapubic cystostomy. *J. Urol.* **45**:467-475, 1941.
6. Kleinberg, S. Osteitis pubis, with report of case in woman. *J. Urol.* **48**:635-641, 1942.
7. Muschat, M. Osteitis pubis following prostatectomy. *J. Urol.* **54**: 447-458, 1945.
8. Cohen, H. H. Osteitis pubis. *J. Urol.* **55**:84-88, 1946.
9. Powell, N. B. Osteitis pubis. *J. Bone & Joint Surg.* **29**:785-787, 1947.
10. Kirz, E. Osteitis pubis after suprapubic operations on bladder: with report of ten cases. *Brit. J. Surg.* **34**:272-276, 1947.
11. Riches, E. W. Treatment of benign enlargement of prostate. *Brit. J. Urol.* **18**:115, 1946.
12. Jones, R. W. *Fractures and Other Bone and Joint Injuries.* 723 pp. Baltimore: Williams & Wilkins Co., 1940.
13. Weinman, J. P., and Sicher, H. *Bone and Bones: Fundamentals of bone biology.* 464 pp. St. Louis: C. V. Mosby Co., 1947.
14. Rosenberg, M. L., and Vest, S. A. Osteitis pubis. *J. Urol.* **60**:767-775, 1948.

WERNER'S SYNDROME*

A Report of Two Cases

JACOB SCHOTT, M.D.,† AND SIDNEY DANN, M.D.‡

BROOKLYN, NEW YORK

OCCASIONALLY the opportunity of seeing one of the rarer disease states or syndromes presents itself to most physicians. Their recognition can be made more readily possible if those who see them bring them to the attention of the profession.

Our purpose in this paper is to add 2 more cases of Werner's syndrome to the literature, to review briefly the more pertinent features of the syndrome and to outline the criteria in as simple a manner as possible, so that they can be easily remembered. Thannhauser,§ in 1945, added 5 cases to the literature and in a most excellent article summarized all that had been published on the subject.

Etiology

The etiology of the disease is not definitely known. The accepted theory at present is that it is due to a defect in the germ plasm that becomes evident in the third or fourth decade of life. That it is a primary endocrine disturbance has been excluded. Although there is not much doubt that an endocrine element is present, this is thought to be secondary and not primary.

Heredity plays a role; there is frequently collateral occurrence in brothers and sisters of one generation.

Diagnosis

Usually the first frank manifestation of the syndrome is premature graying of the hair, soon followed by thinning.

The shortness of stature dates back to the adolescent age. Birth and childhood development are normal, but in the adolescent years these patients do not maintain the expected growth increase.

Not long after the graying of the hair, which usually starts about the age of twenty, the extremities, particularly the lower ones, begin to take on a spindly appearance. Much discussion and investigation of the skin changes has resulted in the conclusion that they are not sclerodermatous in character. From the waxy, taut, atrophic appearance, at first glance one is apt to mistake them for sclero-

*From the Medical Service, Cumberland Hospital (Service of Dr. James Tesler, Dr. J. J. Guttman, director of medicine).

†Associate in medicine, Cumberland Hospital.

‡Assistant in medicine, Cumberland Hospital.

§Thannhauser, S. J. Werner's syndrome (progeria of adult) and Rothmund's syndrome: two types of closely related heredofamilial atrophic dermatoses with juvenile cataracts and endocrine features: critical study with five new cases. *Ann. Int. Med.* **23**:559-626, 1945.

dermatous extremities, but on more careful examination, it is found that the skin can be elevated easily from the subcutaneous structures. It is in the latter structures that the fault lies. The subcutaneous fat tissue is practically absent, and the underlying muscle is extremely thin and atrophic.

Areas of circumscribed hyperkeratoses and ulcerations are not long in appearing, superimposed on the underlying skin changes. That the ulcers are not completely trophic is shown by their readiness in successfully taking a skin graft. The ulcers appear most frequently on areas subjected to pressure: the malleoli of the ankles and over the Achilles tendon, heels and toes. They are due merely to pressure on areas where the skin is tightly drawn over the bone without any protective, subcutaneous fat padding. The hyperkeratotic areas are present chiefly on the soles and over the heels and the heads of the first and fifth metatarsals.

Cataracts fall into the class of juvenile cataracts. Werner, as a student on the ophthalmology wards, first described the occurrence of juvenile cataracts with scleroderma. Star-like opacities develop, mostly on the posterior pole and on the periphery of the lens.

Diabetes may be present in the overt or latent states. There may be only a tendency to this disorder of metabolism as evidenced by abnormal glucose tolerance curves, or the disease may be full blown. Both cases reported below were in diabetic patients, and one, particularly, is rather difficult to control with the usual measures.

Generalized arteriosclerosis is another manifestation of Werner's syndrome. It is the usual type of arteriosclerosis and may result in early complications involving the circulatory system.

Underdevelopment of the sexual organs is a constant finding. Most of the female patients menstruate for some time at least, whereas in the males, erections and the ability to have intercourse are also preserved for a period.

Osteoporosis can readily be demonstrated in roentgen-ray studies of the bones. It has been found, too, in some cases that areas of metastatic calcification exist.

Therapy

In view of the abiotrophic nature of the disease, one cannot hope to accomplish a great deal along curative lines. However, a certain degree of symptomatic improvement can be obtained. The diabetes can be controlled by the usual methods. Generally, the diabetic state in these patients is not too severe, although occasionally they present problems in control. Thyroid should be given for the usual indications of a hypothyroid state. The cataracts may require iridectomy as in the cases reported below. For the skin changes we have been using large doses of components of the vitamin B complex, especially nicotinic acid, with satisfactory results. Some of the tautness of the skin and the immobility of the ankles has been relieved, and the patients have expressed considerable subjective relief. The smaller ulcerations have healed. Larger skin ulcerations are said to respond to grafting.

Finally, in view of the hypogonadism, negative calcium balance, diabetes and increased urinary gonadotropins, it has been suggested that estrogenic therapy be given a trial. We have not used it in our cases.

Case Reports

Case 1. R. W., a 41-year-old woman, was admitted to the hospital on January 25, 1948, complaining of pain and purulent discharge from the right third toe. About 8 months prior to admission the patient had noted pain in the right third toe, which was followed shortly by a moderate amount of purulent discharge from the ulcer at that site. At about the same time small areas of ulceration appeared over the malleoli and the lower tibial regions. The ulcers were quite painful, especially at night, and the patient experienced great difficulty in walking. For an indefinite period, moreover, she had difficulty in walking, although less severe, because of a "high arch," and she wore metal arches in her shoes. Treatment at the hospital afforded some relief, but the symptoms returned shortly after discharge.

The patient had been treated for diabetes for the past 7½ years. She took 15 units of regular insulin and 15 units of protamine zinc insulin in separate syringes in the morning. However, at the age of 23, when bilateral cataracts developed, routine examination of the urine revealed the presence of sugar. At that time she underwent a bilateral cataract extraction. Five years before entry glaucoma had developed in the right eye. Three years later this eye had become infected, and despite the use of penicillin she had lost the vision of that eye.

She had been told on numerous occasions that she had "pituitary and thyroid trouble." From about the age of 15 she had noted that the upper and lower extremities were very thin and that the skin of the extremities was "tight" and hard especially toward the distal regions. She had also noted the development of large "corns" over the bony prominences of the soles of the feet. Ulcerations developed relatively recently as noted above. She had had scattered gray hairs since the age of 32; she studiously dyed these as they appeared, and it was not possible to determine the extent of the canities. The hair had become more sparse in recent years.

In 1943 she noted a mass in the right breast and underwent a radical mastectomy for carcinoma. Since that time she had had no complaints because of the malignant growth.

The menses had begun at the age of 11. The periods occurred every 21 days and lasted for 7 days. The flow was rather profuse. For 2½ years prior to August, 1947, there had been no vaginal bleeding, but at that time she had a period. There was no further vaginal bleeding until her stay on the wards of this hospital, where she had a 3-day period of rather scanty vaginal bleeding. She had been pregnant once, with delivery after 7 months' gestation; the son was 7 years old and in good health. She believed her thinness had been aggravated during this pregnancy. She was legally separated from her husband, who was in a mental institution. She claimed normal libido. There were no symptoms referable to the cardiovascular, respiratory, genitourinary or gastrointestinal systems.

The parents of the patient were first cousins. The father had "kidney trouble" but was otherwise normal. Diabetes had developed in the mother at the time of the menopause, and she had died in diabetic coma at the age of 57; she had had asthma. The parents had no canities or any of the other signs of progeria manifested by the patient. The mother had three sisters, 2 of whom were diabetic and none of whom had gray hair, cataracts or the characteristic habitus of Werner's syndrome. The father had 3 half-sisters, all of whom were alive and well, and 2 brothers; of the latter, 1 had died during an intestinal operation, and the other of carcinoma of the throat. None of the father's siblings manifested the stigmas of the syndrome. The patient has a sister (Case 2) who suffered from similar symptoms. A brother

was completely normal. Three other siblings had died at birth; a fourth had died at the age of 2 weeks.

The patient weighed 102 pounds and was 4 feet, 10 inches in height. Her habitus was strikingly characteristic — spindly arms and legs, with a normally developed trunk. She had the typical bird-like facies resulting from a receding chin, tendency to beaking of the nose and the wearing of powerful lenses in her eyeglasses. Her gait was unsteady because of the atrophy of the muscles of the lower extremities and the high plantar arch, but she walked without any characteristic aberration. Her hair was diffusely sparse and was dyed black. She was of average intelligence and of rather cheerful disposition. No respiratory distress or asthenia was noted.

The right eye showed a buphthalmos (post-glaucoma), and the left a surgical coloboma. Some fibrosis of the lens bed was noted. The fundus seen through a + 15 lens was slightly paler than normal; the vessels were moderately sclerotic, but there were no hemorrhages, exudates or pigmentation. The movements of the extraocular muscles were normal. There was mild circumcorneal injection of the left eye. The teeth were in good condition. The tongue was moist, with well developed papillae. The pharynx was clear. The ears were normal and did not project from the sides of the head in any unusual fashion. The eardrums were also normal. The eyelashes and eyelids were sparse. The voice appeared to be weak and somewhat high pitched (confirmed by the patient's statement), but indirect laryngoscopy did not reveal the hyperemic or keratotic changes described in this condition. The neck was supple. There was no distention of the veins, no tracheal deviation and no palpable thyroid gland.

The lungs were clear to percussion and auscultation. The heart was not enlarged, and the sounds were of fair quality. The aortic second sound was louder than the pulmonic. There was a Grade III, blowing systolic murmur over the entire precordium, maximal over the base; there were no thrills. Sinus rhythm was normal.

The left breast showed normal development; no masses or tenderness was noted. On the right side there was a healed mastectomy scar with no evidence of infiltration or tenderness in this region.

The abdomen was moderately obese and flabby. There was slight tenderness in the right upper quadrant, but no palpable masses or viscera.

Neurologic examination was entirely normal.

There was marked atrophy of the musculature of all the extremities, most pronounced in the distal segments, and this was accompanied by a moderate degree of weakness. The skin also appeared to be atrophic and over some of the terminal phalanges appeared to be tightly bound down to the underlying tissues, although true scleroderma was not present. Owing to the muscular atrophy the bony prominences of the fingers and toes were more prominent. The instep was markedly arched, and the patient used metal arches in her bathroom slippers for ambulation. There was bilateral hallux valgus. Callosities, the size of a 25-cent piece, were noted in the skin over the heads of the first and fifth metatarsals and over the calcaneus; these areas were not tender. On the right medial and the left lateral malleoli there were ulcerations about the size of a dime. These were excavations bordered by corn-like areas similar to those described above. The bases were greyish yellow, and there was no discharge. The areas were quite tender to the touch. Three scabrous callosities were also noted over the lower tibial areas. The tip of the third right toe was reddened, but no discharge was noted. There was no clubbing or edema. There were good pulsations of the posterior tibial and dorsalis pedis vessels.

The skin was dry and atrophic, with a moderate degree of fine scaling. There were no telangiectases, petechiae or jaundice. The nails were well developed but showed evidence of having been bitten. No fat pads were noted. There was a normal distribution of the female hair.

Rectal examination was negative.

Pelvic examination showed a parous introitus. There were no abnormal findings.

The temperature was 98.6°F., the pulse 80, and the respirations 20. The blood pressure was 110/70.

Examination of the blood revealed a red-cell count of 2,500,000, with a hemoglobin of 10 gm. per 100 cc., and a white-cell count of 12,900, with 40 per cent neutrophils and 60 per cent lymphocytes. The sedimentation rate (Linzenmeier method) was 18 mm. in 43 minutes. The urine, which had a specific gravity of 1.010, gave a negative to +++ test for sugar, a negative test for albumin and a negative test for acetone; the sediment contained an occasional white cell. The blood sugar was 103 to 225 mg., the urea nitrogen 15 mg., the calcium 9.5 to 11.0 mg., the phosphorus 3.0 to 6.5 mg., the uric acid 3.4 mg., the creatinine 1.6 mg., and the cholesterol 200 mg. per 100 cc., with 25 per cent cholesterol esters. The total protein was 6.8 gm. per 100 cc., with 4.7 gm. of albumin and 2.1 gm. of globulin, and the carbon dioxide combining power 56 to 68 vol. per cent. The urea clearance was 32 per cent. The phenolsulfonephthalein test showed 45 per cent excretion of the dye in 2 hours. The galactose tolerance test showed the excretion of 3.2 gm. in the urine. The alkaline phosphatase was 1.6 Bodansky units per 100 cc. The cephalin flocculation and Mazzini tests were negative. The basal metabolic rate was +1 per cent.

Oscillometric findings on the left were 2.5 at the wrist, 2 above the ankle, 4 below the knee and 4 above the knee, and on the right, 1.5 at the wrist, 4 above the ankle, 4 below the knee and 4 above the knee.

Electrocardiograms, which revealed a tendency to left-axis deviation (with a small Q wave and isoelectric T wave in Lead 3, inverted T wave in Lead CF_2 and upright but low-voltage T wave in Lead CF_4), were interpreted as showing questionable myocardial damage.

X-ray examination of the chest was negative except for evidence of removal of the right breast. Films of the feet demonstrated marked hallux valgus on the right and a moderate degree on the left. There were no apparent gross abnormalities in the bones of the upper and lower extremities. The hands disclosed normal bone texture and density. Films of the skull showed hyperostosis of the frontal and parietal bones bilaterally. The pituitary fossa was small but within normal limits. There was no evidence of increased intracranial pressure or bone erosion.

The patient was placed on partial bed rest and given 200 gm. of carbohydrate, 75 gm. of protein and 40 gm. of fat. She was fairly well regulated on 15 units of protamine zinc insulin and 15 units of regular insulin given in separate syringes in the morning. She also received the following medications three times daily: nicotinic acid, 200 mg.; vitamin C, 200 mg.; and vitamin B_1, 20 mg. Papaverine, which had been given in doses of 0.1 gm. (1½ gr.) three times daily, was discontinued because of nausea. The patient claimed considerable subjective improvement on this medication; she stated that her legs felt "looser and stronger." The ulcerations healed slowly, leaving thin scabrous lesions. Of course, it is not possible to determine the relative roles played by the bed rest and the medications in the healing of these long-standing lesions. She was placed gradually on an ambulatory status and discharged as "improved" after 7 weeks in the hospital.

Case 2. M. B., a 45-year-old woman, the sister of the patient in Case 1, was admitted to the Cumberland Hospital on February 10, 1948, complaining of chest pain of 2 days' duration. The pain was described as precordial and substernal and continuous in severity, with no radiation. She complained of weakness and had noted dyspnea only on talking. There was no cough, edema or palpitations and no previous similar episodes.

The past history included diabetes of 16 years' duration; the diagnosis had first been made during routine urine examination while the patient was undergoing treatment for a foot infection. The disease had been fairly well controlled on 10 units of regular insulin and 10 units of protamine zinc insulin taken in separate syringes in the morning. Three and a half years prior to admission a cataract developed in the right eye, and this was removed 6 months later. One year before admission a cataract extraction was done on the left eye. Vision had been poor. Glaucoma developed in the right eye postoperatively. The patient had had gray hair since the age of 40. Three years prior to admission ulcers on the legs entirely similar to those described in Case 1, as well as corns over the bony prominences on the soles of the feet, developed. The ulcers were painful, and she had great difficulty in walking. She stated that the legs felt very cold and she was bothered by cold weather.

The menses had begun at the age of 12, occurring every 28 days and lasting 2 or 3 days, during which there was scanty flow. There had been no menses since October, 1947. The patient had had an ectopic pregnancy in 1930, and she had not been pregnant since, although she had attempted to conceive. She claimed normal libido. Prior to admission she had been treated in the Cumberland Hospital Out-Patient Department for diabetes and leg ulcers, receiving for the latter various ointments and vitamin B_1 without benefit.

The resident who first examined this patient thought that she looked vaguely familiar but it was not until the second hospital day, when he found her talking to her sister who was on the ward at the same time, that the diagnosis became evident.

Physical examination revealed slight dyspnea while the patient was talking, but she was otherwise in no distress. She was exactly 5 feet in height and weighed 101 pounds. In appearance she seemed to be the twin of the patient in Case 1, both in facies and in habitus. The hair was scanty and gray. The eyebrows and eyelashes were also scanty. The movements of the extraocular muscles were normal. The scleras were clear. The right eye revealed surgical coloboma. The vessels of the fundus showed minimal sclerotic changes; there were no hemorrhages, exudates or papilledema. The left fundus was obscured by a cataract, although a cataract had been extracted on this side. The ears were normal in size and shape. There were no fat pads of the face or neck. The tongue showed well developed papillae. The pharynx was normal. The voice was normal, and indirect laryngoscopy revealed no changes. The neck was supple, with no distended veins, palpable masses or tracheal deviation. The thyroid gland was not enlarged. The lungs were clear to percussion and auscultation. Examination of the heart showed the point of maximum intensity in the fifth intercostal space within the midclavicular line. The sounds at the apex were distant and poor in quality. There was a soft, blowing systolic murmur at the apex. There were no thrills. The pulmonic second sound was louder than the aortic. There was normal sinus rhythm. The breasts showed normal development, with no masses. There was no rigidity, tenderness or palpable masses in the abdomen. No viscera were palpable. There was a well healed suprapubic midline surgical scar. The extremities were practically identical with those of the patient in Case 1, including atrophy of the muscles and subcutaneous tissue, small superficial ulcers over the right tendo achilles and over the base of the left fifth metatarsal, callosities over the heads of the first and fifth metatarsal bones and calcanei bilaterally and a marked hallux valgus bilaterally. The pulsations of the posterior tibial and dorsalis pedis vessels were excellent. The plantar arches were accentuated. The second, third and fourth fingers of both hands were markedly nodular and somewhat distorted, resembling the gnarled fingers observed in burnt-out rheumatoid arthritis. The joints were only slightly painful on firm palpation. There were slight sclerodermatous-like changes over the terminal phalanges of the fingers. There was normal distribution of the hair. The skin over the extremities was atrophic and slightly scaly. No telangiectatic changes were noted. Neurologic examination disclosed some unsteadiness in gait, as in Case 1, but again this was due to muscular weakness, painful leg ulcers and high plantar arches; there did not appear to be any neurologic background for the difficulties in gait; position sense and so forth was intact. Rectal examination was negative. Pelvic examination revealed a parous introitus. The cervix was pointed anteriorly. The fornices were normal. The fundus was not felt.

The temperature was 99°F., the pulse 105, and the respirations 24. The blood pressure was 114/70.

Examination of the blood disclosed a red-cell count of 4,200,000, with a hemoglobin of 13 gm. per 100 cc., and a white-cell count of 9200, with 52 per cent neutrophils, 45 per cent lymphocytes and 3 per cent monocytes. The hematocrit was 44 per cent. The urine gave a negative to ++ test for sugar and negative tests for albumin and acetone. The blood sugar on three occasions was 142, 181.8 and 200 mg. per 100 cc. The blood urea nitrogen was 12 mg., the uric acid 3.6 and 2.6 mg., the creatinine 1.5 mg., the calcium 11.0 mg., the phosphorus 3.0 mg., and the cholesterol 238 mg. per 100 cc., with 70 per cent cholesterol esters. The total plasma protein was 7.2 gm. per 100 cc., with 5.2 gm. of albumin and 2.0 gm. of globulin. The blood Kline and cephalin flocculation tests were negative. The alkaline phosphatase was 1.0 Bodansky unit per 100 cc. The basal metabolic rate was −27 per cent.

X-ray examination of the chest revealed definite striation of the pulmonary fields, which was possibly due to some peribronchial thickening. There was marked decalcification of the bones of both feet, and considerable hallux valgus formation bilaterally, more marked on the left side, with almost complete inward subluxation of the bases of the proximal phalanges of the great toes from their articulations with the heads of the corresponding metatarsals. The intermetatarsal arteries showed appreciable calcification. There was moderate loss of calcium of all the bones of the carpometacarpal region and of the phalanges of both hands. Examination of the skull demonstrated granular osteoporosis, with neither direct nor indirect evidence of increased intracranial pressure. A small amount of lime was noted in the region of the pineal gland.

An electrocardiogram taken immediately on admission showed only left-axis shift and was identical with one taken 1 year previously in the clinic.

The patient soon ceased to complain of chest pain and, aside from the disability caused by the leg ulcers, was quite comfortable. She was placed on a diet of 200 gm. of carbohydrate, 70 gm. of protein and 50 gm. of fat. She was treated with 15 units of protamine zinc insulin and 30 units of regular insulin mixed in one syringe in the morning. She was not overly co-operative in the matter of diabetic control, additional foodstuffs being found in her bedside table on several occasions; however, this did not seem to disturb her metabolic balance to any significant degree. She received therapy for the leg ulcers similar to her sister's. However, therapy was not administered over as long a period, and the response was not quite so satisfactory; she was discharged as "improved" on the same day as her sister. During her hospital course the temperature, pulse and respirations were within normal limits. A follow-up electrocardiogram showed no significant changes. The sedimentation rate was 55 minutes (Linzenmeier method).

Discussion

It is hardly necessary to review the diagnostic criteria in these cases. A review of them leaves little doubt that they are classic examples of Werner's syndrome. We have had the opportunity of presenting them to Dr. Thannhauser, and he concurred with our diagnosis, stating that they were typical examples of the syndrome. Indeed, our 2 patients look like the twin sisters of the 2 brothers whom Dr. Thannhauser described in his exhaustive review article.

It is important to remember that the syndrome may not develop in all its features but may occur as a *forme fruste*. A knowledge of all the features of the syndrome is necessary to enable one to recognize the incomplete forms. It will be noted that our patients, like those reported elsewhere, were treated for many years by internists, ophthalmologists and general practitioners without the syndrome as a whole being recognized. We are quite sure that the disorder is not so rare as it appears to be. The advantages of the early recognition of a heredofamilial disorder are obvious.

Summary

The criteria of Werner's syndrome are reviewed.

Two cases of this syndrome are reported.

Attention is called to the presence of incomplete forms of this syndrome and the eugenic importance of early recognition of the syndrome in its complete or incomplete forms.

MEDICAL PROGRESS

PERIPHERAL VASCULAR DISEASE*

ROBERT R. LINTON, M.D.†

BOSTON

THIS report considers peripheral vascular disease under the two main divisions of diseases of the arteries and diseases of the veins.

DISEASES OF THE ARTERIES

The surgical treatment of peripheral vascular diseases has made tremendous strides in recent years. The role that the sympathetic nervous system plays in the control of the arterial circulation of the extremities and the benefits derived by sympathetic neurectomy in many conditions are certainly to be included in great advances made in the therapy of peripheral arterial disease. Improvements in surgical technic, especially of blood-vessel anastomoses, the availability of blood transfusions through the establishment of blood banks and the development of the antibiotics, which have practically eliminated serious surgical infections, are other important factors in the widening of the scope of the surgical treatment of all vascular disorders.

Peripheral Arteriosclerosis

Arterial diseases secondary to peripheral arteriosclerosis are increasing in frequency because of the advancing age of the general population. The treatment of these conditions is becoming of ever-increasing importance because of this fact and since they represent one of the degenerative diseases that develop with old age.

The surgical therapy of peripheral arteriosclerosis of the lower extremities has become more of a surgical problem in recent years because of the improvement that can be obtained in the peripheral circulation by lumbar sympathectomy. This is especially true in patients that present themselves for treatment before actual gangrene of the extremity has developed. The chief indication for sympathetic neurectomy in these patients is the demonstration of normal or increased vasoconstriction or vasospasm. Various tests have been described to determine which patients will benefit by this procedure. Morton and Scott[1] used anesthesia, general, spinal or local, to determine vasomotor sympathetic activity. White[2] recommended paravertebral injections of procaine to block the sympathetic nerves. Gibbon and Landis[3] described their method of reflex vasodilatation by heating the unaffected extremities or portions of the body. These tests have been found to be of value in certain cases, but in others in which a negative response is obtained sympathectomy frequently improves the circulation. Smithwick[4] described a test that is simpler and gives consistently more accurate results in determining which patients will benefit by sympathectomy. It consists in exposing the affected limb for an hour at a temperature of 68°F. If the skin temperature of the extremity reaches or approaches room temperature within a few degrees, under these conditions the presence of vasomotor activity is demonstrated and indicates that benefit will be derived from sympathetic neurectomy. Another simple clinical test that has been found of value is the observation of sudomotor activity in the extremity, which usually means that the blood vessels of the extremity will dilate if the vasomotor constrictor impulses are eradicated by an effective sympathetic denervation. Freeman[5] has warned that in certain cases of advanced peripheral arteriosclerosis, especially those without evidence of normal vasoconstriction, sympathectomy may be detrimental because much of the blood may be shunted directly into the veins through the opening up of numerous small arteriovenous anastomoses. Burch[6] and Goetz[7] have recommended the use of a digital plethysmograph as a method of investigating peripheral vascular disease. They believe that with it exact information can be obtained about the degree of occlusion, the degree of vasospasm and the degree of collateral circulation. For practical clinical purposes, the method has not yet been proved, and at present it remains as a laboratory procedure for investigative studies in peripheral vascular disease. Another diagnostic procedure that has been recommended in recent years is arteriography. A roentgenographic visualization by the intra-arterial injection of a radio-opaque substance has been utilized as a diagnostic procedure for a number of years. Various types of solutions have been used. Shumacker[8] and Kleinsasser[9] recommend the use of 35 per cent diodrast solution. Each patient should be tested for sensitivity to the solution before it is employed. Visualization of the chambers of the heart, the pulmonary circulation and the great vessels has been successfully demonstrated by Robb and Steinberg,[10] using 70 per cent diodrast solution. X-ray visualization of the abdominal aorta has been described by Wagner[11] and Nelson.[12] They recommend an 80 per cent sodium iodide solution.

*From the Department of Surgery, Massachusetts General Hospital.

†Assistant clinical professor of surgery, Harvard Medical School; visiting surgeon, Massachusetts General Hospital.

It should be pointed out that arteriography is not without its dangers because of reactions from the drugs, which may in a few cases result in death and, in others, tragic ischemic difficulties in the injected limb. Arteriography should therefore be employed only when indicated and not as a routine in cases of arterial disorders. The most recent method of studying the peripheral arterial circulation is by means of radioactive isotopes. Smith and Quimby[13] first reported the use of sodium 24 to show the level of adequate circulation in a limb and so determine the site of amputation in patients with obliterative arterial disease. Mufson et al.,[14] from the same clinic, used this method to determine the efficacy of drugs used in the treatment of peripheral vascular disease. Elkin and his associates[15] have reported studies to determine the adequacy of peripheral arterial circulation using sodium 24 by intravenous and subcutaneous intramuscular injections. At the present time these studies and reports are extremely interesting, but further investigations with this new technic must be performed before the true value of the method can be determined.

The benefit of sympathectomy in the treatment of peripheral arteriosclerosis has been reported by a number of surgeons during the past year — Hendrick and Aycock,[16] de Takats,[17] Freeman[5] and Yeager and Cowley.[18] A careful selection of the patients subjected to this form of therapy should be made. The younger the patient is and the more evidence there is of vasomotor activity in the extremity, the greater the benefit that will be obtained. Intermittent claudication, as a rule, does not improve spectacularly after sympathectomy, but it has been observed to disappear gradually several years after the operation. The immediate benefit derived by sympathectomy is chiefly in the vascular supply to the integument. This in itself may be of great importance, since it will prevent the breaking down of the skin especially of the toes, which if it occurs frequently results in gangrene necessitating amputation. There appears to be definite evidence, however, not only that the extremity derives an immediate benefit from this form of treatment but also that it is the best protection that can be given to prevent serious vascular disorders with gangrene in old age. In other words, it appears at the present writing that the symptoms and signs of peripheral arteriosclerosis may be reversible if sympathectomy is performed early in the course of the disease and provided the sympathetic neurectomy is sufficiently extensive to prevent regeneration.

In the therapy of peripheral vascular disease there is a constant rivalry between the internist and the surgeon, the former to find nonsurgical methods of therapy to supplant surgical ones, and the latter to develop new surgical procedures. This form of competition should not be discouraged, but unfortunately too frequently some of the methods are reported as the final answer to a problem without a sufficiently critical analysis of the results and procedures used. Both nonsurgical and surgical methods fall into this error. The chief criticism of the latter is that too many unqualified surgeons from lack of study and experience perform, with poor or disastrous results, surgical operations that have been established by authorities in their fields. This naturally discredits the procedure in the eyes both of many of the profession and of the laity. A number of nonspecific substances have been recommended for the improvement of peripheral arterial circulation during the past two decades. Some are given parenterally and others orally. These include the intravenous injection of a hypertonic solution of sodium chloride,[19] or a nonspecific foreign protein (typhoid vaccine)[20] or diethyl oxide (ether)[21]; the intramuscular injection of sodium tetrathionate[22]; the oral administration of cytochrome C[23] or alpha tocopherol (vitamin E)[24]; and finally the subcutaneous injection of histidine combined with the oral administration of ascorbic acid (vitamin C).[25] The beneficial effect on the peripheral circulation obtained by any of these methods, if it occurs, may only be transitory, and in most of the clinical reports other forms of therapy were utilized concomitantly on the patients, so that the improvement in the circulation cannot be attributed entirely to them. Borst and Holleman[26] have recently reported 3 cases of coronary thrombosis in 18 patients treated with intravenous sodium chloride solution and advise against its use.

Chemical sympathectomy by means of adrenolytic and sympatholytic drugs has been utilized for many years without much success, but recently in this country it is being investigated with new drugs that show considerable progress in this field. Acheson and Moe,[27] in 1946, described tetraethylammonium chloride, or bromide, a ganglionic blocking agent. Nickerson and Goodman,[28] also in 1946, reported another drug, dibenamine (dibenzylbetachlorethylaminohydrochloride), which blocks the terminations of the sympathetic motor pathways in smooth muscle. Coller et al.[29] and Lyons and his co-workers,[30] in 1947, reported the effects obtained with tetraethylammonium chloride in the diagnosis and treatment of peripheral vascular disease, including such conditions as causalgia, thromboangiitis obliterans and thrombophlebitis. Both drugs produce peripheral vasodilatation, but their side effects are frequently so disagreeable that their clinical use seems somewhat limited and in some cases dangerous complications have been reported, one recently by Friedlich, Chapman and Stanbury.[31] Priscol (2-benzyl 4, 5-imidazoline hydrochloride) is the most recent of these drugs to be employed in this country, although it was first reported in 1939 by Hartmann and Isler,[32] and since then numerous reports of its clinical use have appeared in the European and South American medical litera-

ture. Grimson,[33] in this country, has recently reported the results in the use of this drug in a variety of peripheral vascular diseases, including Raynaud's disease, peripheral arteriosclerosis, thromboangiitis obliterans, popliteal aneurysms, causalgia, acute arterial occlusion and venous thrombosis. It may be administered intravenously, intramuscularly or orally in doses of 25 to 75 mg. The results are sufficiently encouraging to warrant further investigation and clinical trial, but as yet it seems doubtful that a panacea for all these vascular diseases has been found. Chemotherapy for peripheral arterial diseases may eventually supplant sympathetic neurectomy, but at the present writing the latter, because of its more lasting effects and in most cases its few disadvantages, remains the best form of therapy in the majority of cases. Intermittent venous occlusion by the use of a pneumatic tourniquet cuff on the extremity, although of value in acute arterial occlusions, seems to have little if any benefit in the treatment of peripheral arteriosclerosis.

Despite the recent development of sympathectomy in the treatment of peripheral arteriosclerosis, amputations must still be performed in a certain number of patients. Improvements in technic are still being devised in the various types of amputations. Holden[34] again draws attention to the increased morbidity and mortality with toe amputations performed in this group of patients, many of whom require major thigh amputations because of failure to heal after the toe amputations. McKittrick,[35] on the other hand, has recently recommended transmetatarsal amputation in patients with gangrene secondary to lesions involving the toes in the diabetic patient with peripheral arteriosclerosis. This has proved to be a great advance in the surgical treatment of these patients, since it obviates an amputation at a higher level and preserves the foot with a surprisingly good functional result. He admits that the indications for this type of amputation are not yet completely clear, but they are continuing to be extended until a careful follow-up study of all patients satisfactorily demonstrates a clear-cut conception regarding whether it should or should not be undertaken. He points out that the use of this type of procedure has been greatly extended through the use of penicillin. Alldredge[36] reviews the surgery of amputations and reports some of the technics of specific procedures. Silbert[37] recommends that the lower-leg amputation should be used more frequently than a mid-thigh or low-thigh amputation, since he claims that it reduces the mortality and because of preservation of the knee joint results in better function. Pearl[38] describes a modification of the supracondylar Callander type of amputation.

Thromboangiitis Obliterans

Thromboangiitis obliterans, or Buerger's disease, is the most common obliterative arterial disease that affects the young male. Freeman[39] reported that the diagnosis was made in 274 of 3778 patients admitted to all the vascular centers during World War II. It is still a rare disease in the female. Only one probable case has been seen in a woman in the Peripheral Vascular Clinic of the Massachusetts General Hospital since it was organized in 1928. It rarely affects the Negro race, but in the last year Davis[40] and Breidenbach and Palmer[41] have reported it in several Negroes. It is generally agreed that in the earlier cases sympathetic ganglionectomy offers the patient the best form of surgical therapy.[42] Desensitization of the foot by means of crushing the peripheral nerves to it, described by Smithwick and White,[43] is still an important method of treatment in patients who present painful ulcerating lesions of the toes. This form of therapy not only relieves the patient of pain but also produces an improvement in the circulation since it sympathectomizes the limb distal to the level at which the nerves are crushed. Smoking, although not a definite etiologic factor, results in the progression of the disease in the majority of cases even in the sympathectomized extremity. Freeman[39] reports that in 77 patients who stopped smoking completely, there was progression of the disease in only 2, whereas in a group of 16 who admitted further smoking there was progression in 8. Adrenolytic and sympatholytic drugs, including tetraethylammonium chloride or bromide, dibenamine and priscol, are being used in various clinics in the nonsurgical treatment of this disease. Encouraging reports are appearing in the literature regarding this form of therapy, but as yet their true value has not been determined. It seems doubtful that they will replace sympathectomy, since the effect is only transient, whereas if the sympathectomy is performed properly a permanent vasodilatation is obtained.

Raynaud's Disease

Raynaud's disease characteristically affects the young and emotional person and is seen most frequently in women. Since the disease seems to be the result of an increased vasomotor activity in the sympathetic nervous system in a majority of cases and in only a few due to a local fault in the arterioles of the fingers, sympathectomy is the best form of surgical therapy. A preganglionic type of sympathetic neurectomy, as described by Smithwick,[44] is still the most generally accepted method of treatment. The results obtained for the upper extremity have not proved so lasting as those for the lower extremity.[45] For this reason further investigations are in progress in an attempt to improve the type of sympathectomy for the upper extremity. It is believed that a more radical and extensive ablation of the lower cervical and upper dorsal portions of the sympathetic nervous system should be performed. At the present time an attack on this problem along these lines is being car-

ried out in the Peripheral Vascular Clinic at the Massachusetts General Hospital. The adrenolytic and sympatholytic drugs are also being used for the treatment of this condition in many clinics. As in thromboangiitis obliterans, the results are somewhat encouraging, but the benefits derived persist only as long as the drug is used. Because of the high percentage of recurrence following the usual dorsal sympathectomy, these drugs are considered in a more favorable light than surgery in a number of clinics that are using them. Further experience is necessary, however, to determine their true value as a permanent form of therapy.

Peripheral Arterial Embolism and Thrombosis

Peripheral arterial embolism occurs most frequently in patients with auricular fibrillation and after acute myocardial infarction. The diagnosis as a rule is not difficult, but it is important to differentiate this disease from acute arterial thrombosis. The latter develops as a rule in elderly patients with advanced arteriosclerosis. The treatment of the latter should consist of conservative nonsurgical measures, such as the use of the anticoagulants heparin and dicumarol, and intermittent venous occlusion. Peripheral arterial embolism, on the other hand, is primarily a surgical disease in a majority of cases, and even a saddle embolus at the bifurcation of the aorta may be successfully removed, as demonstrated in recent years by a number of surgeons (Murray,[46] Linton,[47] Keeley[48] and Tendler[49]). The most satisfactory surgical approach to peripheral emboli is a direct one to expose the artery at the point of embolization, even those of the aorta, as demonstrated by the above reports. Warren and Linton,[50] in 1948, reviewed the results in 179 arterial emboli in 98 patients. Surgical embolectomy saved 85.7 per cent of 21 limbs, whereas 65.8 per cent were preserved by conservative treatment. Arterial embolism is a true emergency, since if treatment, either surgical or conservative, is withheld for more than eight to ten hours the incidence of gangrene is greatly increased, owing to the formation of a distal propagated thrombosis from the site of embolism; if this condition develops, no therapy will re-establish the circulation to the limb.[51] Surgical embolectomy should be considered and immediately performed provided a competent vascular surgeon is available. If not, conservative treatment with the anticoagulants and intermittent venous occlusion should be instituted at once.[52] The patient should not be first subjected to the latter therapy and if it is not successful then turned over to the surgeon. Leriche[53] has recently reported the successful resection of the bifurcation of the aorta for arterial thrombosis of this large blood vessel. This appears to be a heroic procedure for a condition that might respond well to adequate lumbar sympathectomy. Therapeutic venous occlusion or the interruption of the concomitant vein, when a major artery is severed, was first recommended by Makins[54] in 1919. During World War I it was ordered to be performed for major arterial injuries, whereas in World War II the benefit seemed so doubtful that it was not so ordered and was performed only in a relatively small number of cases.[55] A great deal of experimental work has been done to evaluate the effect of this procedure. At the present time there is experimental evidence that the blood inflow to an extremity is diminished using indirect measurements of blood flow,[56] whereas by means of direct methods utilizing the Rein thermostromuhr an actual increase has been observed.[57] The clinical application of therapeutic venous occlusion, utilizing the method of intermittent venous occlusion by means of a pneumatic venous tourniquet, has saved extremities that otherwise would have been lost from gangrene.[58] Its chief value is for extremities with an acute arterial occlusion, such as arterial embolism or arterial thrombosis, and it deserves a definite place in the therapy of such conditions. It must be begun within a few hours of the vascular accident; otherwise, intra-arterial thrombosis distal to the point of occlusion will result, and gangrene will develop regardless of the therapy used. It is probably of little or no benefit in the therapy of chronic or obliterative arterial diseases, such as that seen in peripheral arteriosclerosis and thromboangiitis obliterans. It is believed that the beneficial effect obtained by the Pavaex (passive vascular exercise) method of Hermann and Reid[59] can best be explained by the fact that it probably causes intermittent venous occlusion.

Blood-Vessel Surgery

The recent interest in blood-vessel surgery to produce arterial and venous shunts has stimulated the experimental evaluation of the relative merits of the nonsuture and suture method of blood-vessel anastomoses. Blakemore and Lord[60] deserve much credit for stimulating surgeons in the practicability of blood-vessel repair and anastomosis utilizing the nonsuture vitallium-tube method. However, the results in the armed forces using it in battle injuries during World War II[55, 61-63] were not outstanding because of the difficulty in getting the patient early, the necessity of working under battle conditions and, probably not least, the lack of training of the surgeons in this branch of surgery who had to use it under these conditions. Nevertheless, the method, at least in acute arterial injuries of the young, deserves a place in the field of vascular surgery and should not be completely discarded.

The use of absorbable fibrin tubes instead of vitallium ones for vein anastomoses has been advocated by Swenson and Gross[64] and reported results are extremely good, thrombosis having occurred in only 1 case out of 27. The availability of this type of tube for general use, however, seems

doubtful. Johns[65] compared the results of the suture and the nonsuture method for the anastomosis of veins in animals. He reported 90 per cent functioning patent end-to-side splenorenal anastomoses and 73 per cent end-to-end ones, utilizing the suture technic, whereas with the nonsuture vitallium tube method only 17 per cent were patent in a group of end-to-end splenorenal anastomoses. There seems little doubt that in venous anastomoses at least the suture technic is preferable because it reduces the danger of thrombosis from a relatively low differential pressure between the blood vessels and the slow rate of blood flow. It also permits the construction of an end-to-side anastomosis, which is not so feasible with the nonsuture technic. The use of the everting type of mattress suture to produce an intima-to-intima approximation in the anastomosis is recommended by most surgeons.[65, 66] The vessels must also be of sufficient caliber; otherwise thrombosis results in the majority of cases.[66] The utilization of rapid freezing permits the preservation of blood vessels indefinitely so that it is recommended that blood-vessel banks be established. The recent experimental work of Williamson and Mann[67] throws some doubt on the feasibility of such a project, since they report good results with autogenous transplantations of both arteries and veins, whereas they found that homogeneous transplantations are not justified in the light of present knowledge. Gross et al.,[68] however, have reported that chemically preserved blood vessels may be of value to bridge arterial defects.

Aneurysms and Arteriovenous Fistulas

Numerous papers reporting large series of aneurysms and arteriovenous fistulas have appeared in the recent surgical literature, the results of vascular injuries from missiles in World War II[55, 61-63, 69] and treated in the vascular centers established by the United States Army Medical Department. The advances in the treatment of these conditions have been chiefly through the utilization of sympathectomy to enhance the collateral circulation[70] and also in various types of blood-vessel repair and anastomoses. Another advance in the treatment of arteriovenous fistulas is that a number of surgeons have expressed the opinion and also demonstrated that if possible the continuity of an artery should be maintained[71-73] because the generally accepted method of treatment by quadruple ligation with excision of the fistula, although it restores normal vascular physiology of the body and preserves the limb, is always followed by a diminished blood flow to the extremity. The surgical therapy of the degenerative type of aneurysm secondary to arteriosclerosis has received added impetus because the incidence of it in various sites of the arterial system seems definitely to be on the increase. One of the most noteworthy contributions has been made by Blakemore,[74] who used a method of wiring and electrothermic coagulation. Whenever possible the restoration of a pulsating arterial blood flow to an extremity, after the removal of an aneurysm, should be attempted, as a number of surgeons have demonstrated.[71-73] Blakemore[75] has adapted the nonsuture method of blood-vessel anastomosis, using the vitallium-tube cuffs and a vein graft inlay in the operation of restorative endoaneurysmorrhaphy for popliteal aneurysm. The external reinforcement of the aneurysmal wall by the application of cellophane has received considerable attention, since a number of apparently successful results have been reported.[76, 77] The true evaluation of the method, however, must await further experience and time. The application of cellophane around an artery proximal to an aneurysm for the purpose of gradual occlusion of the vessel has been attempted,[78] but the results have not been outstanding. Elkin[79] has recently re-emphasized the fact that aneurysms and arteriovenous fistulas may develop secondary to surgical procedures and warns against mass ligation of arteries and veins, especially transfixion sutures. Linton[80] has recently reported, as others have, the dire effects in the conservative treatment of the arteriosclerotic type of popliteal aneurysm and demonstrated the value of a preliminary sympathectomy followed later by an aneurysmectomy in the treatment of this condition.[81-83]

The surgical treatment of congenital hemangioma in cases in which the area involved is not great is a simple procedure, but it is still a challenge to the surgeon if the lesion is an extensive one, when improvement rather than a cure is the best result that can be obtained.[84]

Chronic lymphedema is the one peripheral vascular lesion in which little if any progress has been made since Kondoleon described his radical method of surgical excision of the diseased subcutaneous tissues. Minor modifications of this method appear now and then,[85] but further investigations and study are necessary to improve the results of the present forms of therapy, which at best are none too good.

Diseases of Veins

Varicose Veins

Varicose veins of the lower extremity constitute one of the most common ailments affecting man. Therapy for this condition in the past for the most part has been inadequate because of recurrence or persistence of the varicosities. The injection of sclerosing solutions, it is generally agreed, gives only temporary benefit even when combined with a high saphenous interruption. It should be pointed out that this form of therapy also is not without its dangers. Boyd and Robertson[86] have reported that deep thrombophlebitis and incompetence of the communicating veins in the lower extremity may develop, and Vaughn and Lees,[87] in 1947, collected

44 cases of fatal pulmonary embolism following injection therapy. Smith and Johnson,[88] in 1948, reported from the Mayo Clinic 17 nonfatal pulmonary emboli and 1 death following this treatment in 11,700 patients. In the same year Luke and Miller[89] collected 4 additional fatal cases and 10 other cases of deep thrombophlebitis after ligation and injection of the saphenous vein. Accidents following the operative treatment have also occurred. Luke and Miller[89] also report several cases of ligation of the femoral artery or vein instead of the saphenous vein, and in 1 case injection of the distal femoral artery with the sclerosing solution resulting in gangrene of the extremity. Many similar unreported accidents have occurred undoubtedly. (I know of 6 patients in whom the femoral artery was ligated and divided instead of the saphenous vein.) The procedure of high interruption of the saphenous vein should not be condemned because of these mistakes since they were the result of poor surgery. New types of sclerosing solutions continue to appear in the surgical literature. The most recent one, sotradecol (sodium tetradecyl sulfate),[90] has certain advantages over the older ones, but it will not cure varicose veins without surgical removal of the main saphenous trunks. High interruption with retrograde injection of the sclerosing solution perhaps gives better results than injection therapy alone, but few patients obtain permanent relief. Because of the poor results by these forms of therapy, there has been during the past few years the revival by a few surgeons (Hodge,[91] Prioleau,[92] Vaughn,[93] Summers,[94] Sherman[95] and Linton[96]), of high interruption and removal of the saphenous veins, both long and short, by stripping or excision. The stripping of varicosities was first recommended by Mayo[97] and Babcock.[98] The intraluminal type of stripper described by the latter has proved to be the more satisfactory, since with its use the vein can be removed more readily and completely. Unfortunately, many patients will continue to have the injection treatment, only to come finally to the surgeon for more radical therapy. The results in these cases are never so good as those in the patients who have not been treated with injections, since it is often difficult to remove the saphenous veins completely because of local areas of fibrosis and obliteration, which prevent insertion of the stripper and the complete removal of the main saphenous trunks. In addition the valves of the communicating veins, especially in the lower leg, become incompetent, the result of the sclerosing solution damaging these structures, so that in these patients recurrences are more prone to develop. It is my opinion that the most satisfactory therapy is ligation of the long saphenous vein at the saphenofemoral junction with the removal of the main trunk of this vein by stripping from the groin down to a point just distal to the internal malleolus. In a few cases excision of some of the large tortuous varices may be necessary, and in some the saphenous trunk may be bifid, in which case both are removed. If the short saphenous vein is incompetent it should be removed also, after ligation at the saphenopopliteal junction, by stripping it to the level of the external malleolus. The stripping procedure is best performed under a general anesthetic to obtain the most radical removal of these veins. In most cases only a few injections of a sclerosing solution are necessary in the few remaining varicosities. These, for the most part, are for cosmetic effect.

Simple Varicose Ulcers

The cure of simple varicose ulcers due to varicose veins, in essence, consists of eradication of the varicosities. Numerous types of ointments have been recommended for the cure of this condition, but none, even those including the antibiotics and sulfonamides, have any special virtues. The use of these drugs should be discouraged since their topical application frequently sensitizes the patient to them so that their parenteral use at a later date, when they are needed for serious infections, may be prohibited owing to an acquired sensitization.

Post-Thrombotic Varicose Ulcers

The cure of this distressing type of ulceration remains a serious problem. Numerous methods of therapy have been recommended but few give better than temporary healing. The application of a gelatin-paste (Unna) boot or an elastic adhesive bandage (elastoplast) will heal, at least temporarily, the majority of these ulcers. These methods should be used chiefly to prepare the extremity for surgery by healing the ulcer and as postoperative dressings for periods of a few weeks to months. A new type of operation recently developed for the less extensive ulcers includes interruption of the superficial femoral vein, with ligation and stripping of the long and short saphenous veins. Buxton and Coller[99] and Homans[100] were the first to suggest interruption of the femoral veins. Linton and Hardy[96] have reported good results in a number of patients combining superficial femoral-vein interruption with radical stripping of the long and short saphenous veins. Further experience and a longer follow-up study on these cases are needed before a true evaluation of this method can be obtained. The method described in 1917 by Homans,[101] consisting of radical excision of the ulcer with an immediate split-thickness skin graft, still deserves a place in this field of surgery, especially in the large indolent ulcers. The superficial femoral vein should be interrupted also if this procedure is performed, and the saphenous veins removed if they are large and incompetent. In some cases a less disfiguring operation, described by Linton[102] in 1938, has given excellent results. The operation has been modified somewhat since it was originally described. These

modifications consist of interruption of the superficial femoral vein, ligation and stripping of the long saphenous vein, excision of the short saphenous vein and a partial excision of the deep fascia of the lower leg, only one incision being used on the inner side of the lower leg.

Venous Thrombosis and Pulmonary Embolism

During the last decade great interest has been shown in the prevention and treatment of venous thrombosis and pulmonary embolism. No longer is the attitude tenable that death from massive embolism is inevitable in a certain number of medical and surgical patients, or that expectant conservative treatment is satisfactory. Carlotti et al.,[103] in 1947, showed that pulmonary embolism and infarction occurred more frequently in medical than surgical patients, and also that 87 per cent of a series of 273 medical patients were over forty years of age. This agrees with Allen et al.,[104] who showed that in 367 surgical patients with thromboembolism 82 per cent were in the same age group. Despite the fact that most cases of thromboembolic disease occur in middle-aged or elderly patients the young are not immune, as demonstrated by Zuschlag[105] and Myers and Artsis,[106] who report the occurrence of thromboembolism in children under fifteen years of age. Fatal embolism in this age group, however, is rare.

Pulmonary embolism from other sources is recognized. Of special interest are articles that have appeared in the last year reporting cases of maternal pulmonary embolism by contents of the amniotic fluid.[107-109] The majority of the patients die, and the diagnosis is not made until autopsy. The condition apparently is rare, but it may be more common than it appears, since in one hospital 3 patients died from this cause and they represented all the maternal deaths occurring during one year.[108] Ingersoll and Robbins,[110] in 1947, called attention again to the danger of oil embolism following hysterosalpingography.

Prophylaxis. Greater attention should be directed to the prophylaxis of venous thrombosis because deaths from massive pulmonary embolism still occur in patients without clinical evidence of deep venous thrombosis. Evans[111] reports 54 deaths from fatal embolism under these conditions in a series of 238 cases of postoperative thromboembolism, an incidence of 23 per cent. Allen,[112] in 1947, demonstrated the value of prophylactic interruption of the femoral vein in a series of 458 patients over sixty-five years of age, as compared to a comparable group of patients who received no special prophylactic therapy. In the former there was 1 death from massive pulmonary embolism, whereas in the latter there were 26 deaths from the same cause. At the present time there are no statistics that demonstrate that prophylactic use of dicumarol or heparin will give the same or better protection in this aged group of patients in which thromboembolism is so prone to develop. Allen,[112] Bishop[113] and Golodner et al.[114] have drawn attention to the relatively high incidence of fatal embolism in elderly patients with fractured hips, and recommend prophylactic measures such as interruption of the femoral vein or the use of anticoagulants. Veal[115] has stressed the importance of interruption of the femoral vein in thigh amputations for the prevention of pulmonary embolism.

The prophylactic use of dicumarol has also been demonstrated to be of value in the average postoperative patient. Smith and Mulligan[116] reported its use in 2353 surgical patients with only 1 death from fatal embolism. Allen[117] reported the effect of dicumarol in 647 patients between forty and sixty-five years of age undergoing major surgical operations, without a single death from pulmonary embolism. Barker et al.[118] and Murray,[119] in 1947, likewise reported 100 per cent protection by the prophylactic use of the anticoagulants in the postoperative patient. It should be pointed out, however, that the use of dicumarol in this manner is not without its dangers, since Allen[112] reports 2 deaths and Smith[116] 1 from hemorrhage.

Treatment. Homans,[120] in 1934, was the first to recommend interruption of the femoral vein for the treatment of venous thrombosis and pulmonary embolism. Since then numerous articles on the subject have appeared in the surgical literature. Allen and his associates[121] at the Massachusetts General Hospital have demonstrated the efficacy of bilateral femoral-vein interruption in the treatment of venous thrombosis and the prevention of massive pulmonary embolism by this method. Other surgeons[122-125] agree that this method is of value, especially in patients who have had nonfatal pulmonary emboli, to prevent fatal embolism. Carlotti et al.[103] also showed a reduction in the over-all mortality in cardiac patients with thromboembolic disease who were subjected to bilateral femoral-vein interruption, as compared to a control group not so treated.

It should be emphasized that interruption of the femoral vein if performed by capable surgeons is a safe procedure, but it is not without its dangers for the average surgeon, as pointed out by Sarnoff,[126] who reports a case of gangrene of both legs following the procedure. Dennis[127] also reports serious impairment of the circulation after interruption of the common femoral vein and the saphenous vein in the same extremity. It is believed that if femoral-vein interruption is to be performed, the interruption should never include the common femoral vein and the saphenous vein, since under these circumstances there may be insufficient collateral venous return from the extremity, as demonstrated in the report by Dennis.[127] In competent hands it is recommended that if a clot is found in the common femoral vein, the interruption of this vessel be performed after thrombectomy distal to the saphenofemoral

junction and proximal to the origin of the profunda femoris vein. If no clot is found, in the majority of cases interruption of the superficial femoral vein just distal to the profunda femoris will suffice. Interruption of the inferior vena cava is chiefly indicated, as pointed out by a number of authorities,[128-131] for pulmonary emboli arising from pelvic thrombophlebitis, especially the septic variety. It should not be performed for the usual case of thromboembolic disease, since it is a major surgical procedure that may carry a relatively high mortality, as demonstrated by Thebaut,[132] and in most cases it is an interruption of the venous system at a level higher than necessary to prevent further pulmonary emboli.

The treatment of deep venous thrombosis by procaine block of the lumbar sympathetic nerves, as recommended by Ochsner,[133] is of chief value in patients with the obstructing type of femoroiliac thrombosis to relieve pain and swelling. It does not necessarily protect the patients from pulmonary embolism.

The use of the anticoagulants in the treatment of thromboembolism has received great impetus also, especially since dicumarol has become so readily available. Heparin was the first anticoagulant to be used and is still recommended by some authorities (Murray,[119] Bauer,[134] Jorpes,[135] Loewe[136] and Evans[111]). The chief exponents of heparin have been in the Canadian and Swedish schools. Loewe,[136] in this country, has developed a preparation that is slowly absorbed and is given intramuscularly. Despite the fact that it is the ideal anticoagulant yet developed because of its rapidity of action and its ease of control, heparin has not found wide usage on account of its expense. Dicumarol, more recently discovered, is now more generally used because it is cheap and may be given orally.[118, 137, 138] It is generally agreed that it should not be used unless laboratory facilities are available for the accurate determination of the prothrombin time. It is significant to note that deaths still occur from massive pulmonary embolism in clinics that treat patients with the anticoagulants after a diagnosis of venous thrombosis with or without pulmonary embolism has been made.[109, 118, 136-141] The same drawback to the treatment by femoral-vein interruption has also been reported by Allen[117] in a large series of cases, so that at the present time there is no method that will prevent massive pulmonary embolism in 100 per cent of the patients. In conclusion, it appears that the safest method of treatment, once thromboembolism has developed and is recognized in any patient, is to perform bilateral femoral-vein interruptions and to supplement this treatment by anticoagulant therapy.

Portal Hypertension with Bleeding Esophageal Varices

One of the important advances in peripheral vascular surgery in the last few years has been the treatment of bleeding esophageal varices secondary to a portal bed block, either of the intrahepatic type (portal cirrhosis) or the extrahepatic (the so-called Banti's syndrome) by the construction of various types of venous shunts between the portal and the general venous systems. Whipple[142] and Blakemore[143] deserve great credit for this renewed attack on a problem that has long baffled the medical profession. They first recommended as the operative procedure a splenectomy, a left nephrectomy and an end-to-end nonsuture anastomosis between the splenic and renal veins. In 1947 the operation was modified by an end-to-side suture type of splenorenal anastomosis with preservation of the kidney as recommended by Linton et al.[144] Direct anastomoses between the portal vein and the inferior vena cava, both end-to-side and side-to-side, have been performed safely a number of times by Blakemore.[145] Further experience and observations of these patients with portacaval shunts are necessary before a true evaluation of this form of treatment can be determined. Furthermore, the relative merits of splenorenal, end-to-side portacaval and side-to-side portacaval anastomoses have yet to be determined. It appears quite definite, however, that a surgeon should not perform a splenectomy alone for bleeding esophageal varices, especially of the extrahepatic (Banti) type, since this may be the only opportunity at which a satisfactory venous shunt can be performed.[146]

References

1. Morton, J. J., and Scott, W. J. M. Methods for estimating degree of sympathetic vasoconstriction in peripheral vascular diseases. *New Eng. J. Med.* **204**:955-962, 1931.
2. White, J. C. Diagnostic blocking of sympathetic nerves to extremities with procaine: test to evaluate benefit of sympathetic ganglionectomy. *J. A. M. A.* **94**:1382-1388, 1930.
3. Gibbon, J. H., Jr., and Landis, E. M. Vasodilatation in lower extremities in response to immersing forearms in warm water. *J. Clin. Investigation* **11**:1019-1036, 1932.
4. Smithwick, R. H. Surgical intervention on sympathetic nervous system for peripheral vascular disease. *Arch. Surg.* **40**:286-306, 1940.
5. Freeman, N. E., Leeds, F. H., and Gardiner, R. E. Sympathectomy for obliterative arterial disease: indications and contraindications. *Ann. Surg.* **126**:873-894, 1947.
6. Burch, G. E. New sensitive portable plethysmograph. *Am. Heart J.* **33**:48-75, 1947.
7. Goetz, R. H. Rate and control of blood flow through skin of lower extremities. *Am. Heart J.* **31**:146-182, 1946.
8. Shumacker, H. B., Jr., and Godley, A. F. Arteriography in cases of aneurysm and arteriovenous fistula: with review of literature concerning choice of solution. *Yale J. Biol. & Med.* **20**:273-289, 1948.
9. Kleinsasser, L. J. Peripheral arteriography. *Surgery* **22**:930-944, 1947.
10. Robb, G. P., and Steinberg, I. Visualization of chambers of heart, pulmonary circulation and great blood vessels in man: summary of method and results. *J. A. M. A.* **114**:474-480, 1940.
11. Wagner, F. B., Jr. Arteriography in renal diagnosis: preliminary report and critical evaluation. *J. Urol.* **56**:625-635, 1946.
12. Nelson, O. A. Arteriography in diagnosis of upper abdominal conditions. *Northwest Med.* **44**:314-322, 1945.
13. Smith, B. C., and Quimby, E. H. Use of radioactive sodium in study of peripheral vascular disease. *Ann. Surg.* **125**:360-371, 1947.
14. Mufson, I., Quimby, E. H., and Smith, B. C. Use of radioactive sodium as guide to efficacy of drugs used in treatment of diseases of peripheral vascular system: preliminary report. *Am. J. Med.* **4**: 73-82, 1948.
15. Elkin, D. C., et al. Study of peripheral vascular disease with radioactive isotopes. Part 1. *Surg., Gynec. & Obst.* **87**:1-8, 1948.
16. Hendrick, J. W., and Aycock, T. B. Sympathectomy for peripheral vascular disease. *South. M. J.* **40**:219-228, 1947.
17. de Takats, G., and Evoy, M. H. Sympathectomy for peripheral vascular sclerosis. *J. A. M. A.* **133**:441-445, 1947.

18. Yeager, G. H., and Cowley, R. A. Anatomical observations on lumbar sympathetics with evaluation of sympathectomies in organic peripheral vascular disease. *Ann. Surg.* **127**:953-967, 1948.
19. Silbert, S. Treatment of thrombo-angiitis obliterans by intravenous injections of hypertonic salt solution: preliminary report. *J. A. M. A.* **86**:1759-1761, 1926.
20. Allen, A. W., and Smithwick, R. H. Use of foreign protein in treatment of peripheral vascular diseases: results of intravenous injections of typhoid vaccine. *J. A. M. A.* **91**:1161-1168, 1928.
21. Katz, R. A. Impending ischemic gangrene: new non-surgical therapeutic suggestions (preliminary report). *New Orleans M. & S. J.* **98**:542-555, 1946.
22. Theis, F. V., and Freeland, M. R. Thromboangiitis obliterans: treatment with sodium tetrathionate and sodium thiosulfate. *Arch. Surg.* **40**:190-207, 1940.
23. Proger, S., and Dekaneas, D. J. Clinical use of cytochrome C in patients with intermittent claudication. *Bull. New Eng. M. Center* **8**:145-147, 1946.
24. Shute, E. V., Vogelsang, A. B., Skelton, F. R., and Shute, W. E. Influence of vitamin E on vascular disease. *Surg., Gynec. & Obst.* **86**:1-8, 1948.
25. Wirtshafter, Z. T., and Widmann, R. Elaboration of histamine in vivo in treatment of peripheral vascular disorders: preliminary report. *J. A. M. A.* **133**:604, 1947.
26. Borst, J. R., and Holleman, E. J. W. Myocardial infarction resulting from intravenous administration of hypertonic solution of sodium chloride to patients with arteriosclerosis obliterans of lower extremities: report on three cases. *Acta. med. Scandinav.* **130**: 26-36, 1948.
27. Acheson, G. H., and Moe, G. K. Action of tetraethylammonium ion on mammalian circulation. *J. Pharmacol. & Exper. Therap.* **87**:220-236, 1946.
28. Nickerson, M., and Goodman, L. S. Physiological properties of new series of sympatholytic agents. *Federation Proc.* **5**:194, 1946.
29. Coller, F. A., et al. Tetraethylammonium as adjunct in treatment of peripheral vascular disease and other painful states. *Ann. Surg.* **125**:729-755, 1947.
30. Lyons, R. H., et al. Effects of blockade of autonomic ganglia in man with tetraethylammonium: preliminary observations on its clinical application. *Am. J. M. Sc.* **213**:315-323, 1947.
31. Friedlich, A. L., Jr., Chapman, W. P., and Stanbury, J. B. Severe reaction to tetraethylammonium chloride. *New Eng. J. Med.* **238**: 629, 1948.
32. Hartmann, M., and Isler, H. Chemische Konstitution und pharmakologische Wirksamkeit von in 2-Stellung substituierten Imidazolinen. *Arch. f. exper. Path. u. Pharmakol.* **192**:141-154, 1939.
33. Grimson, K. S., Reardon, M. J., Marzoni, F. H., and Hendrix, J. P. Effects of priscol on peripheral vascular diseases, hypertension and circulation in patients. *Ann. Surg.* **127**:968-991, 1948.
34. Holden, W. D. Arteriosclerotic ischemic necrosis of lower extremities. *Surgery* **22**:125-128, 1947.
35. McKittrick, L. S. Recent advances in care of surgical complications of diabetes mellitus. *New Eng. J. Med.* **235**:929-932, 1946.
36. Alldredge, R. H. Major amputations. *Surg., Gynec. & Obst.* **84**: 759-764 (No. 4A), 1947.
37. Silbert, S. Mid-leg amputations for gangrene in diabetic. *Ann. Surg.* **127**:503-512, 1948.
38. Pearl, F. Atraumatic low thigh amputation: further modification of and experiences with technique. *Surg., Gynec. & Obst.* **87**: 308-312, 1948.
39. Freeman, N. E. Diagnosis and treatment of thromboangiitis obliterans in vascular centers of army general hospitals. *Am. Heart J.* **33**:332-340, 1947.
40. Davis, H. A., and King, L. D. Comparative study of thromboangiitis obliterans in white and Negro patients. *Surg., Gynec. & Obst.* **85**:597-603, 1947.
41. Breidenbach, W. C., Jr., and Palmer, D. M. Thromboangiitis obliterans in Negro: report of case and review of literature. *Am. Heart J.* **33**:849-855, 1947.
42. Cooper, F. W., Jr., and Harris, M. H. Sympathectomy in treatment of thrombo-angiitis obliterans. *South. Surgeon* **14**:70-81, 1948.
43. Smithwick, R. H., and White, J. C. Peripheral nerve block in obliterative vascular disease of lower extremity: further experience with alcohol injection or crushing of sensory nerves of lower leg. *Surg., Gynec. & Obst.* **60**:1106-1114, 1935.
44. Smithwick, R. H. Problem of producing complete and lasting sympathetic denervation of upper extremity by preganglionic section. *Ann. Surg.* **112**:1085-1100, 1940.
45. Haxton, H. A. Regeneration after sympathectomy and its effects on Raynaud's disease. *Brit. J. Surg.* **35**:69-76, 1947.
46. Murray, G. Aortic embolectomy. *Surg., Gynec. & Obst.* **77**:157-162, 1943.
47. Linton, R. R. Arterial embolism: simplified technique for removal of saddle embolus at bifurcation of aorta with report of successful case. *Surg., Gynec. & Obst.* **80**:509-516, 1945.
48. Keeley, J. L. Saddle embolus of aorta: report of successful embolectomy. *Ann. Surg.* **128**:257-265, 1948.
49. Tendler, M. J. Aortic embolectomy: case report. *Memphis M. J.* **23**: 109-111, 1948.
50. Warren, R., and Linton, R. R. Treatment of arterial embolism. *New Eng. J. Med.* **238**:421-429, 1948.
51. Linton, R. R. Peripheral arterial embolism: discussion of postembolic vascular changes and the r relation to restoration of circulation in peripheral embolism. *New Eng. J. Med.* **224**:189-194, 1941.
52. Allen, E. V. Emergency treatment of vascular occlusions. *J. A. M. A.* **135**:15-17, 1947.
53. Leriche, R., and Morel, A. Syndrome of thrombotic obliteration of aortic bifurcation. *Ann. Surg.* **127**:193-206, 1948.
54. Makins, G. H. *On Gunshot Injuries to the Blood Vessels.* 251 pp. New York: William Wood & Co., 1919.
55. DeBakey, M. E., and Simeone, F. A. Battle injuries of arteries in World War II: analysis of 2,471 cases. *Ann. Surg.* **123**:534-579, 1946.
56. Halperin, M. H., Friedland, C. K., and Wilkins, R. W. Effect of local compression upon blood flow in extremities of man. *Am. Heart J.* **35**:221-237, 1948.
57. Linton, R. R., Morrison, P. J., Ulfelder, H., and Libby, A. L. Therapeutic venous occlusion: its effect on arterial inflow to extremity as measured by means of Rein thermostromuhr. *Am. Heart J.* **21**: 721-742, 1941.
58. Linton, R. R. Treatment of acute arterial occlusion by means of intermittent venous occlusion: report of case. *Arch. Surg.* **46**: 395-403, 1943.
59. Hermann, L. G., and Reid, M. R. Passive vascular exercises: treatment of peripheral obliterative arterial diseases by rhythmic alternation of environmental pressure. *Arch. Surg.* **29**:697-704, 1934.
60. Blakemore, A. H., and Lord, J. W., Jr. Nonsuture method of blood vessel anastomosis: experimental and clinical study. *J. A. M. A.* **127**:685-691 and 748-753, 1945.
61. Rose, C. A., Hess, O. W., and Welch, C. S. Vascular injuries of extremities in battle casualties. *Ann. Surg.* **123**:161-179, 1946.
62. Mustard, W. T. Technic of immediate restoration of vascular continuity after arterial wounds: indications and results. *Ann. Surg.* **124**:46-59, 1946.
63. Stewart, C. F. War experiences with nonsuture technic of anastomosis in primary arterial injuries. *Ann. Surg.* **125**:157-170, 1947.
64. Swenson, O., and Gross, R. E. Absorbable fibrin tubes for vein anastomoses. *Surgery* **22**:137-143, 1947.
65. Johns, T. N. P. Comparison of suture and nonsuture methods for anastomosis of veins. *Surg., Gynec. & Obst.* **84**:939-942, 1947.
66. Shumacker, H. B., Jr., and Lowenberg, R. I. Experimental studies in vascular repair. I. Comparison of reliability of various methods of end-to-end arterial sutures. *Surgery* **24**:79-89, 1948.
67. Williamson, C. S., and Mann, F. C. Functional survival of autografts and homogenous transplants of blood vessels: experimental study. *Arch. Surg.* **54**:529-540, 1947.
68. Gross, R. E., Hurwitt, E. S., Bill, A. H., Jr., and Peirce, E. C., 2nd. Preliminary observations on use of human arterial grafts in treatment of certain cardiovascular defects. *New Eng. J. Med.* **239**: 578, 1948.
69. Elkin, D. C., and Warren, J. V. Arteriovenous fistulae: their effect on circulation. *J. A. M. A.* **134**:1524-1528, 1947.
70. Shumacker, H. B., Jr. Sympathetic denervation of extremities: operative technique, morbidity and mortality. *Surgery* **24**: 304-325, 1948.
71. Freeman, N. E. Arterial repair in treatment of aneurysms and arteriovenous fistulae: report of eighteen successful restorations. *Ann. Surg.* **124**:888-919, 1946.
72. Shumacker, H. B., Jr. Problem of maintaining the continuity of artery in surgery of aneurysms and arteriovenous fistulae. *Ann. Surg.* **127**:207-230, 1948.
73. Heringman, E. C., Rives, J. D., and Davis, H. A. Repair of arteriovenous fistulas: evaluation of operative procedures and analysis of fifty-three cases. *J. A. M. A.* **133**:663-668, 1947.
74. Blakemore, A. H. Clinical behavior of arteriosclerotic aneurysm of abdominal aorta: rational surgical therapy. *Ann. Surg.* **126**: 195-207, 1947.
75. *Idem.* Restorative endoaneurysmorrhaphy by vein graft inlay. *Ann. Surg.* **126**:841-849, 1947.
76. Poppe, J. K. Cellophane treatment of syphilitic aneurysms with report of results in six cases. *Am. Heart J.* **36**:252-256, 1948.
77. Rea, C. E. Surgical treatment of aneurysm of abdominal aorta. *Minnesota Med.* **32**:153-156, 1948.
78. de Takats, G., and Reynolds, J. T. Surgical treatment of aneurysms of abdominal aorta. *Surgery* **21**:443-454, 1947.
79. Elkin, D. C. Aneurism following surgical procedures: report of five cases. *Ann. Surg.* **127**:769-779, 1948.
80. Linton, R. R. Arteriosclerotic popliteal aneurysm: report of 14 cases treated by preliminary lumbar sympathetic ganglionectomy and aneurysmectomy. *Surgery* (in press).
81. Bird, C. E. Sympathectomy as a preliminary to obliteration of popliteal aneurisms: with suggestion as to sympathetic block in cases of ligature, suture, or thrombosis of large arteries. *Surg., Gynec. & Obst.* **60**:926-929, 1935.
82. Richards, R. I., and Learmonth, J. R. Lumbar sympathectomy in treatment of popliteal aneurysm. *Lancet* **1**:383, 1942.
83. Lilly, G. D. Management of aneurysms of lower extremities. *Ann. Surg.* **123**:601-606, 1946.
84. Elkin, D. C., and Cooper, F. W., Jr. Extensive hemangioma: report of case. *Surg., Gynec. & Obst.* **84**:897-902, 1947.
85. Poth, E. J., Barnes, S. R., and Ross, G. I. New operative treatment for elephantiasis. *Surg., Gynec. & Obst.* **84**:642-644, 1947.
86. Boyd, A. M., and Robertson, D. J. Treatment of varicose veins: possible danger of injection of sclerosing fluids. *Brit. M. J.* **2**: 452-454, 1947.
87. Vaughn, A. M., and Lees, W. M. Fatal pulmonary embolism following varicose vein injection: report of case and review of literature. *J. A. M. A.* **118**:1293-1296, 1942.
88. Smith, F. L., and Johnson, M. A., III. Incidence of pulmonary embolism after venous sclerosing therapy. *Minnesota Med.* **31**: 270-272, 1948.

89. Luke, J. C., and Miller, G. G. Disasters following operation of ligation and retrograde injection of varicose veins. *Ann. Surg.* **127**: 426-431, 1948.
90. Dingwall, J. A., Lin, D. T. W., and Lyon, J. A. Use of sodium tetradecyl sulfate in sclerosing treatment of varicose veins: experimental and clinical study. *Surgery* **23**:599-601, 1948.
91. Hodge, G. B., Grimson, K. S., and Schiebel, H. M. Treatment of varicose veins by stripping, excision and evulsion. *Ann. Surg.* **121**: 737-750, 1945.
92. Prioleau, W. H. Varicose veins: treatment by excision preferable to treatment by ligation and injection. *J. South Carolina M. A.* **43**:359-361, 1947.
93. Vaughn, A. M. Multiple retrograde saphenous vein ligation and phlebectomy with aid of malleable intraluminal guide. *Surgery* **21**: 851-860, 1947.
94. Summers, J. E. Technique of operation for varicose veins. *Am. J. Surg.* **76**:72-75, 1948.
95. Sherman, R. S. Varicose veins: anatomic findings and operative procedure based upon them. *Ann. Surg.* **120**:772-784, 1944.
96. Linton, R. R., and Hardy, I. B., Jr. Postthrombotic syndrome of lower extremity: treatment by interruption of superficial femoral vein and ligation and stripping of long and short saphenous veins. *Surgery* **24**:452-468, 1948.
97. Mayo, C. H. Treatment of varicose veins. *Surg., Gynec. & Obst.* **2**:385-388, 1906.
98. Babcock, W. W. New operation for extirpation of varicose veins of leg. *New York M. J.* **86**:153-156, 1907.
99. Buxton, R. W., and Coller, F. A. Surgical treatment of long-standing deep phlebitis of leg. II. Supplementary report. *Surgery* **18**: 663-669, 1945.
100. Homans, J. Late results of femoral thrombophlebitis and their treatment. *New Eng. J. Med.* **235**:249-253, 1946.
101. *Idem.* Etiology and treatment of varicose ulcer of leg. *Surg., Gynec. & Obst.* **24**:300-311, 1917.
102. Linton, R. R. Communicating veins of lower leg and operative technic for their ligation. *Ann. Surg.* **107**:582-593, 1938.
103. Carlotti, J., Hardy, I. B., Jr., Linton, R. R., and White, P. D. Pulmonary embolism in medical patients: comparison of incidence, diagnosis and effects of treatment in two hundred and seventy-three cases at Massachusetts General Hospital in two five-year periods (1936 to 1940 and 1941 to 1945 inclusive). *J. A. M. A.* **134**:1447-1452, 1947.
104. Allen, A. W., Linton, R. R., and Donaldson, G. A. Thrombosis and embolism: review of 202 patients treated by femoral vein interruption. *Ann. Surg.* **118**:728-740, 1943.
105. Zuschlag, E. Infarction of lung in children. *Am. J. Dis. Child.* **74**: 399-416, 1947.
106. Myers, H. L., and Artsis, N. Bilateral nontraumatic iliofemoral thrombophlebitis in child. *Am. Heart J.* **36**:295-298, 1948.
107. Goodof, I. I. Maternal pulmonary embolism by amniotic fluid: report of case. *J. Maine M. A.* **38**:101, 1947.
108. Gross, P., and Benz, E. J. Pulmonary embolism by amniotic fluid: report of three cases with new diagnostic procedure. *Surg., Gynec. & Obst.* **85**:315-320, 1947.
109. Hemmings, C. T. Maternal pulmonary embolism by contents of amniotic fluid. *Am. J. Obst. & Gynec.* **53**:303-306, 1947.
110. Ingersoll, F. M., and Robbins, L. L. Oil embolism following hysterosalpingography. *Am. J. Obst. & Gynec.* **53**:307-311, 1947.
111. Evans, J. A., and Dee, J. F. Anticoagulant treatment of postoperative venous thrombosis and pulmonary embolism. *New Eng. J. Med.* **238**:1-5, 1948.
112. Allen, A. W. Interruption of deep veins of lower extremities in prevention and treatment of thrombosis and embolism. *Surg., Gynec. & Obst.* **84**:519-527, 1947.
113. Bishop, H. F. Thrombosis-embolism problem associated with hip fractures in aged. *Geriatrics* **3**:26-34, 1948.
114. Golodner, H., Morse, L. J., and Angrist, A. Pulmonary embolism in fractures of hip. *Surgery* **18**:418-423, 1945.
115. Veal, J. R. Prevention of pulmonary complications following thigh amputations by high ligation of femoral vein. *J. A. M. A.* **121**: 240-244, 1943.
116. Smith, G. Van S., and Mulligan, W. J. Dicumarol prophylaxis against venous thrombosis in women undergoing surgery. *Surg., Gynec. & Obst.* **86**:461-464, 1948.
117. Allen, A. W. Present evaluation of prophylaxis and treatment of venous thrombosis and pulmonary embolism. *Surgery* (in press).
118. Barker, N. W., Hines, E. A., Kvale, W. F., and Allen, E. V. Dicumarol: its action, clinical use and effectiveness as anticoagulant drug. *Am. J. Med.* **3**:634-642, 1947.
119. Murray, G. Anticoagulant therapy with heparin. *Am. J. Med.* **3**: 468-471, 1947.
120. Homans, J. Thrombosis of deep veins of lower leg causing pulmonary embolism. *New Eng. J. Med.* **211**:993-997, 1934.
121. Allen, A. W., Linton, R. R., and Donaldson, G. A. Venous thrombosis and pulmonary embolism. *J. A. M. A.* **133**:1268-1276, 1947.
122. Homans, J. Operative treatment of venous thrombosis in lower limbs. *Am. J. Med.* **3**:345-354, 1947.
123. Ochsner, A. Venous thrombosis. *Surgery* **24**:445-451, 1948.
124. Colby, F. H. Prevention of fatal pulmonary emboli after prostatectomy. *J. Urol.* **59**:920-930, 1948.
125. Elkin, D. C. Venous thrombosis of extremities. *South. Surgeon* **14**: 61-69, 1948.
126. Sarnoff, J. Gangrene of both legs following femoral vein ligation. *New York State J. Med.* **48**:1480-1482, 1948.
127. Dennis, C. Disaster following femoral vein ligation for thrombophlebitis; relief by fasciotomy; clinical case of renal impairment following crush injury. *Surgery* **17**:264-269, 1945.
128. Gaston, E. A., and Folsom, H. Ligation of inferior vena cava for prevention of pulmonary embolism: report of two cases. *New Eng. J. Med.* **233**:229-233, 1945.
129. Veal, J. R., Hussey, H. H., and Barnes, E. Ligation of inferior vena cava in thrombosis of deep veins of lower extremities. *Surg., Gynec. & Obst.* **84**:605-610, 1947.
130. Collins, C. G., Jones, J. R., and Nelson, E. W. Surgical treatment of pelvic thrombophlebitis: ligation of inferior vena cava and ovarian veins: preliminary report. *New Orleans M. & S. J.* **95**: 324-329, 1943.
131. Moses, W. R. Ligation of inferior vena cava or iliac veins: report of thirty-six operations. *New Eng. J. Med.* **235**:1-7, 1946.
132. Thebaut, B. R., and Ward, C. S. Ligation of inferior vena cava in thromboembolism: report of 36 cases. *Surg., Gynec. & Obst.* **84**: 385-401, 1947.
133. Ochsner, A. Use of vasodilatation in treatment of venous thrombosis. *Surg., Gynec. & Obst.* **84**:659-664, 1947.
134. Bauer, G. Heparin therapy in acute deep venous thrombosis. *J. A. M. A.* **131**:196-203, 1946.
135. Jorpes, J. E. Anticoagulant therapy in thrombosis. *Surg., Gynec. & Obst.* **84**:677-681, 1947.
136. Loewe, L. Anticoagulant therapy with heparin-Pitkin menstruum in thromboembolic disease. *Am. J. Med.* **3**:447-467, 1947.
137. Cosgriff, S. W., Cross, R. J., and Habif, D. V. Management of venous thrombosis and pulmonary embolism. *S. Clin. North America* **28**:324-340, 1948.
138. Allen, E. V. Clinical use of anticoagulants: report of treatment in 1,686 postoperative cases. *J. A. M. A.* **134**:323-329, 1947.
139. Borgstrom, S. Value of postoperative dicoumarin prophylaxis at early rising. *Acta chir. Scandinav.* **96**:47, 1947.
140. Zilliacus, H. On specific treatment of thrombosis and pulmonary embolism with anticoagulants, with particular reference to postthrombotic sequelae: results of five years' treatment of thrombosis and pulmonary embolism at series of Swedish hospitals during years 1940-1945. *Acta. med. Scandinav.* Supp. 171:1-221, 1946.
141. Cummine, H., and Lyons, R. N. Study of intravascular thrombosis with some new conceptions of mechanism of coagulation. *Brit. J. Surg.* **35**:337-363, 1948.
142. Whipple, A. O. Problem of portal hypertension in relation to hepatosplenopathies. *Ann. Surg.* **122**:449-475, 1945.
143. Blakemore, A. H., and Lord, J. W., Jr. Technic of using vitallium tubes in establishing portacaval shunts for portal hypertension. *Ann. Surg.* **122**:476-489, 1945.
144. Linton, R. R., Jones, C. M., and Volwiler, W. Portal hypertension: treatment by splenectomy and splenorenal anastomosis with preservation of kidney. *S. Clin. North America* **27**:1162-1170, 1947.
145. Blakemore, A. H. Indications for portacaval anastomosis-analysis of cases. *Surg., Gynec. & Obst.* **84**:645-653, 1947.
146. Linton, R. R. Portacaval shunts in treatment of portal hypertension: with special reference to patients previously operated upon. *New Eng. J. Med.* **238**:723-727, 1948.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35161

PRESENTATION OF CASE

A ten-year-old girl was admitted to the hospital because of a progressive swelling in the neck.

She was seen for the first time five months before admission in the Out-Patient Clinic. The cervical mass, then of two months' duration, had not been accompanied by any systemic symptoms. There was no change in weight, appetite or bowel habit. No unusual sweating was noted, nor was there any preference for cold or warm weather. There was no tremor or exophthalmos. The patient is said to have frequently cleared her throat "as though she had some obstruction" after the mass appeared, but she had no difficulty swallowing. Two years before admission her mother noted that the patient's emotional pattern had changed: she became unhappy, cried easily and was "less peppy" than she had previously been. These changes persisted.

The patient's mother had had a goiter during pregnancy and for some months thereafter. She received 5 drops of an iodine solution daily for about a year altogether. Iodine was taken during the entire period of pregnancy.

The patient's maternal grandfather had had an operation for hyperthyroidism.

On examination the thyroid gland was diffusely enlarged and not nodular. The left lateral lobe was more easily palpable than the others. There were no other abnormal findings. The temperature was 97.8°F., the weight 66 pounds, and the height 53 inches. X-ray examination of the wrists demonstrated that the bone age was not at variance with the chronologic age. The blood cholesterol was 200 mg. per 100 cc.

The patient was seen regularly in the Out-Patient Department. The mass in the neck persisted and increased in size. Three weeks before admission the gland was diffusely and evenly enlarged. The right lobe, particularly the upper pole, was prominent. The enlargement was firm and granular. Lymph nodes were enlarged, two Delphian and one of the posterior chain on each side. On the same day the decision was made to admit the patient for a surgical biopsy and possibly a more extensive procedure.

On admission the child was quiet and sad, crying on the slightest provocation. The thyroid gland was estimated to be twice its normal size, diffusely enlarged, granular and firm. There was no generalized lymphadenopathy.

The temperature was 99°F., the pulse 86, and the respirations 20. The blood pressure was 98 systolic, 68 diastolic. The height was 54 inches, and the weight 64 pounds.

The urine was normal. The white-cell count was 5600, with a normal differential. The hemoglobin was 12.9 gm. After a barium swallow the esophagus was questionably displaced to the left in the region of the thyroid gland. There was no obstruction to the flow of barium through the esophagus and no evidence of any substernal extension of the thyroid gland.

In the opinion of the last examiner in the Out-Patient Clinic there was definite change in the gland during the three-week interval. It was smaller, and only the right upper pole retained its abnormality; the isthmus and left-lobe processes had receded. The Delphian node and the enlargement of the right-posterior-triangle lymph node persisted.

Operation was deferred in lieu of further clinical observation. Radioactive iodine was administered. There was a 39 per cent uptake in the gland, which was interpreted as the upper limit of normal.

She was discharged on the third hospital day.

Second admission (ten weeks later). During the interval the patient was followed in the Out-Patient Department. Several observers felt that the thyroid gland progressively increased in size during subsequent weeks. She gained about 5 pounds and felt well.

Except for the findings in the neck, there were no changes on physical examination.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. J. H. MEANS: This the first time at one of these conferences that I have been given a case that seems to be goiter. Perhaps it is not a goiter, but it appears to be.

I will make a few comments on the history; then if there is other evidence, we will ask for it and attempt to make a diagnosis. It is apparently clear that this girl had a goiter. I do not believe we need consider other enlargements in the neck. Let us say that it was a goiter. The descriptions fulfill that definition perfectly well. It is interesting that she had no symptomatic changes early in the history, but a change of personality is described. She had crying and depression, which might be seen in Graves's disease. There is little else to suggest Graves's disease, however. Whether or not the mother had a goiter during pregnancy is not perfectly clear. I think that any physician who has a patient going through pregnancy with a thyroid

enlargement does well to give iodine, particularly if there is any evidence of hyperfunction during pregnancy, more than would be explained by the pregnancy itself. I also have the feeling that when women who are pregnant have low metabolism they should be given thyroid. I cannot get any more out of that information than just that, nor can I place any great amount of weight on the fact that the patient's maternal grandfather had an operation for hyperthyroidism. I would like to know more about the family situation, however. I would like to know where the patient was born, where her parents were born and where this operation on her grandfather was done. I would like to know also whether she did or did not come from an endemic goiter region.

DR. BENJAMIN CASTLEMAN: Both she and her mother were born in Massachusetts.

DR. MEANS: We do not know where in Massachusetts, but we know that the goiter region in Massachusetts is in the Berkshires, where minimal thyroid enlargement has been found among school children.

DR. CASTLEMAN: She came from Cambridge.

DR. MEANS: It is stated that the thyroid gland was enlarged and not nodular. It is important to know whether it was a diffuse goiter or a nodular goiter. We have to take this story at face value; it was diffusely enlarged, and no nodules were felt.

Laboratory examination showed a blood cholesterol within normal limits. The finding of enlarged lymph nodes is of importance, the so-called Delphian node. One of the students suggested calling it that to Dr. Cope. The point was that since the Delphian oracle foretold things, and the node just above the isthmus may enlarge when some process is going on in the thyroid gland, it is a tell-tale node. Sometimes one confuses an enlarged pyramidal lobe with a lymph node. I assume that there were enlarged nodes and some of them were in the posterior triangle. Also quite important is the negative evidence that no adenopathy was found elsewhere. There is no mention of splenomegaly or hepatomegaly or anything of that kind. The radioactive-iodine collection was at the upper border of normal, and I will say that it probably was normal. I will conclude, therefore, from that much of the history and the physical findings and that one bit of laboratory evidence, that this patient had a goiter causing no disturbance in function — that is, a state of euthyroidism. I wonder why they sent her in for a biopsy and out without having it done. That is not clear. I wonder why they waited for ten weeks. Perhaps the family refused or it took them ten weeks to convince those in charge that it was indicated. Is that a fair question?

DR. CASTLEMAN: Can you answer that, Dr. Talbot?

DR. NATHAN B. TALBOT: I was anxious to have a biopsy done, but it was difficult to persuade the surgeons.

DR. MEANS: All I can say, then, is that I do not know why they sent her in for a biopsy and then did not do it, because it might have made the diagnosis. The most important thing in diseases of the thyroid gland, as of any other part of the body, is to establish a diagnosis. When one sees an enlarged thyroid gland, particularly when it is not giving rise to any change in function, one almost always has to have a histologic examination. That is the only way to determine its character. If one is dealing with a full-blown picture of Graves's disease, one knows what the thyroid gland will show and does not have to worry about the histologic diagnosis. There are no other laboratory tests recorded in this history, such as the protein-bound iodine. I suppose they were normal, but if they were not done, I would not worry about them because the clinical evidence for euthyroidism is quite impressive. I do not know what was going on during the ten weeks' observation when the gland was smaller, not larger. I do not know how to interpret that. I do not know from the record whether or not the goiter was larger at the time of operation than at the time the patient was first seen. Is that a fair question? Whether it had increased in size or remained stationary is all important in making a differential diagnosis.

DR. TALBOT: There were differences of opinion about the size of this gland as time progressed.

DR. MEANS: It is evident that it was not growing at a great speed. I do not believe they said whether or not it was tender.

DR. TALBOT: It was not tender.

DR. MEANS: They finally did an operation. Whether it was a biopsy or a radical neck resection, I do not know. There was a surgical procedure, which, I suppose, disclosed a diagnosis. What must we consider? I think we have to consider every kind of goiter in differential diagnosis. I will try to be brief. I think we can rule out Graves's disease. The question whether or not it is endemic goiter would come up, but I would dismiss it because she did not come from an endemic region. A goiter due to cabbage or goitrogenic drugs might be considered. Did she have any of these things?

DR. TALBOT: No.

DR. MEANS: Another possibility is tuberculosis of the thyroid gland. I cannot exclude that. I do not know whether we have ever seen a case at this clinic. It is extraordinarily rare. We are now down to some kind of neoplasia or some kind of chronic inflammatory process. It seems to me this case could be one of the forms of chronic thyroiditis such as Hashimoto's struma or Riedel's struma. It could be any one of a considerable variety of tumors. One thinks of primary tumors, of course, although metastatic tumor to the thyroid gland does occur. We have had 2, I think perhaps 3, cases of hypernephroma that metastasized to the thyroid gland. When I was in California a year ago I was told of a

case in which it was proved that a cancer of the colon had metastasized to the thyroid gland. Lymphoma may involve the thyroid gland diffusely and apparently without much lymphoma elsewhere, so that lymphoma must be considered. There is one type of non-neoplastic disease that must be mentioned — that is, amyloidosis. We have had 4 or 5 cases of amyloid disease of the thyroid gland. I do not believe that amyloidosis was present in this case. In fact, I will rule it out, although we have no right to rule it out absolutely because there has been nothing said about a Congo-red test. Amyloidosis of the thyroid gland might be part of what we call idiopathic amyloidosis, but I would expect lesions elsewhere. A chronic, suppurative process or tuberculosis we cannot throw out, but I think it is entirely unlikely.

Of the primary tumors of the thyroid gland I do not believe it is any kind of benign tumor because I would expect that to be nodular, at least in the beginning. Benign tumors of the thyroid gland do not start, in my experience, as a diffuse process. They may become so later by multiplicity of nodules closing together to give the appearance of a diffuse lesion. I think that is unlikely, and I therefore believe the diagnosis lies between some kind of chronic thyroiditis and some kind of malignant tumor, which might be epithelial. There are various types of adenocarcinoma of the thyroid gland, papillary and otherwise, and some highly undifferentiated cancers. I do not think we need to go into the classification of the various types of tumor because one cannot possibly make a differentiation except histologically. As between chronic thyroiditis and a malignant process the regional lymph nodes strongly suggest a malignant process, but we have found the Delphian node, so-called, in chronic thyroiditis, so that that is not absolutely of differential diagnostic value. The mass has never been tender so far as we know. Sometimes these chronic processes are not. There is nothing in the story suggesting an acute thyroiditis, but our general concept of the chronic forms is that they are not an aftermath of an acute type but an independent condition, generally of a different etiology in all probability. As between the two types I have mentioned, the lymphadenoid type of chronic thyroiditis or Hashimoto's struma and Riedel's struma, I would think that the former was more likely simply because it is more common. The Riedel type is very rare, and the description of this gland does not sound like it. It is not described as stony hard. It was firm and granular. I do not know what is meant by granular. I never felt a thyroid gland that I would call granular. The choice lies, I believe, between Hashimoto's struma and some kind of malignant goiter, but I have not the faintest idea which it was. It was not growing very rapidly, which would make it possible to rule out a highly undifferentiated cancer. The regional lymph nodes are frequently involved in papillary types of thyroid cancer, but I would not rule out lymphoma even in the absence of a lymphoma elsewhere. So I am going to leave it as a choice between Hashimoto's struma and a rather diffuse malignant tumor of the thyroid gland, and I think on the chances, a papillary adenocarcinoma would be more likely than any other kind. I am prepared to be told, however, that it is either or neither of them. What is needed here is histologic evidence so far as I am concerned.

DR. CASTLEMAN: Are the x-ray films helpful?

DR. STANLEY M. WYMAN: They are not contributory.

DR. TALBOT: Like Dr. Means, we came to the conclusion that this child probably had either thyroiditis or a neoplasm of the thyroid gland. Not wishing to run the risk of neglecting a neoplasm while it still might be amenable to therapy, we urged surgical biopsy examination. In this connection we also thought that should the diagnosis turn out to be thyroiditis, there might be some prophylactic value in excising a portion of the thyroid isthmus since there is some tendency for thyroiditis to result in constriction of the trachea and adjacent structures. Perhaps Dr. Means would like to comment on this subject.

DR. MEANS: About the matter of constriction from chronic thyroiditis, particularly the Riedel type, it may produce severe tracheal obstruction, but so may the Hashimoto type and a partial resection may have to be done to remove pressure symptoms. This child apparently was getting slight pressure symptoms. In this type of goiter, if it is Hashimoto's, being a lymphadenoma type of thing, one might get good results with x-ray therapy. One does not operate on Hashimoto's struma unless there is an indication for relieving pressure.

That was one other point I did not discuss much. It puzzled me a little whether this posterior gland was part of the same process or a red herring. I was not sure.

DR. TALBOT: It was just posterior to the thyroid gland itself.

DR. MEANS: Quite close to the thyroid gland. I suppose that would favor a little bit the diagnosis of a malignant process because I would expect one might find a Delphian node with thyroiditis, but I would not expect it so much in the lateral region. Another thing is that the gland in Hashimoto's struma is sometimes described as being more or less like an ameba, with pseudopodia sticking out. One can feel scallops at the edge of it, and that is not mentioned here so I am a little bit more inclined to think that it was malignant but I am not at all sure. That just gives it a little edge.

CLINICAL DIAGNOSIS

Chronic thyroiditis, Hashimoto type?
Carcinoma of thyroid gland?

Dr. Means's Diagnosis

Carcinoma of thyroid gland?
Chronic thyroiditis, Hashimoto type?

Anatomical Diagnoses

Chronic thyroiditis, Hashimoto type.
Hyperplasia of thyroid gland.

Pathological Discussion

Dr. Castleman: I am sorry that Dr. Cope is not here. He operated on the patient and first exposed some lymph nodes that were grayish white and slightly firm, but he did not believe they were neoplastic and at operation he favored chronic thyroiditis. The isthmus of the pyramidal lobe and part of the left lobe were excised and they also appeared grayish white. We performed a frozen section on the thyroid gland and found no neoplasia but a Hashimoto struma, and I will show the sections from it. This is the low-power view showing a uniform infiltration with lymphoid germinal centers throughout the thyroid gland. Of particular interest is the condition of the acini, which are definitely hyperplastic. The epithelium is high, and there is scalloping of the colloid, which is quite common in hyperplasia. It is not unusual to find actual hyperplasia in the early stages of Hashimoto struma. One theory of the pathogenesis of Hashimoto struma is that it is really a burned-out hyperthyroidism; this may be an early stage. Ordinarily patients with this disease are women between forty and fifty years of age; in these cases we may not see as much germinal center formation but more of a diffuse lymphocytic infiltration, with compression and replacement of colloid acini, which may give rise to a low basal metabolic rate and myxedematous signs and symptoms.

Dr. Means: Another possible explanation would be compensatory hyperplasia due to the fact that the infiltrative process had destroyed the rest of the parenchyma. The remnant became hyperplastic to take care of the function. In the older patient did you find any areas of hyperplastic parenchyma?

Dr. Castleman: Not usually. The older patient tends to develop myxedema.

Dr. Means: That is when all the parenchyma is knocked out, and there is nothing left to become hyperplastic. That was another point in differential diagnosis between cancer and chronic thyroiditis. If one can prove that there is hypothyroidism, it is real evidence in favor of chronic inflammation rather than cancer, because cancer, no matter how diffuse, rarely knocks out the parenchyma completely with resulting myxedema.

Dr. Castleman: This patient did not have a basal metabolic rate before operation. One month following operation a basal metabolic rate is recorded as −4 per cent.

Dr. Allan M. Butler: Do you endorse the diagnostic biopsy, Dr. Means?

Dr. Means: Yes.

CASE 35162

Presentation of Case

A forty-nine-year-old woman was admitted to the hospital because of joint and muscle pains.

Two weeks prior to admission the patient developed a sudden sharp pain in the right anterior thigh that extended down to the knee. Two days later a similar pain developed in the left anterior thigh and sacroiliac region. Aspirin seemed to relieve most of the pain, but she took as much as 0.6 gm. (10 gr.) four or five times a day. Several days before entry she stopped the medication because of the development of ringing in the ears and nausea. Four days prior to admission both calves became stiff and tender, and the temperature rose to 101°F. Two days before entry a swelling, redness, some pain and tenderness occurred over the left internal malleolus, and a similar swelling occurred on the right heel on the day before admission.

There was no history of previous joint or muscle pains. She was said to be sensitive to house dust. She denied ever having taken sulfonamides.

Physical examination revealed a fairly comfortable woman, with a warm, moist skin. There was a blotchy, erythematous rash about the elbows, left wrist (1 to 3 cm. in diameter) and the left internal malleolus. These areas were not indurated or elevated. There was a soft, Grade II systolic murmur at the apex. There was slight bilateral calf tenderness and a soreness of the heels.

The temperature was 103°F., the pulse 120, and the respirations 24. The blood pressure was 120 systolic, 68 diastolic.

Examination of the blood disclosed a hemoglobin of 14.6 gm. and a white-cell count of 13,200, with 70 per cent neutrophils, 27 per cent lymphocytes, 2 per cent monocytes and 1 per cent basophils. Frequent band forms were seen. The platelets appeared normal. The urine gave a ++++ test for albumin, with a specific gravity of 1.022, and the sediment contained as many as 20 red blood cells and 25 white blood cells per high-power field.

Sulfadiazine therapy was begun on admission. The erythematous blotches on the skin appeared to come and go from hour to hour. On the second hospital day 2000 cc. of dextrose in physiologic saline solution and 200 cc. of sodium lactate were given. The urinary output decreased to 250 cc. on this day, and simultaneously the patient appeared to go into acute cardiac decompensation. Digitalis and other measures were required. The temperature continued to remain elevated up to 102°F., and on the third

day penicillin was started and the sulfadiazine discontinued. During the next two to three days the urine output dropped to 60 cc. per day, and the nonprotein nitrogen was found to be 60 mg. per 100 cc. At this time the carbon dioxide was 24.5 milliequiv. per liter, and the sulfadiazine level was 13.2 mg. per 100 cc. The total protein was 5.9 gm. per 100 cc. The prothrombin time was 33 seconds (normal, 16 seconds). The clotting time was 18 minutes, and the clot retraction was normal. The joint pains, which had been quite bothersome, began to subside, and the temperature returned to near normal. The nonprotein nitrogen continued to rise, being 90, 106 and 150 mg. per 100 cc. on the fifth, sixth and seventh hospital days. The urinary output was still low (150 cc. per day), and disorientation was a prominent symptom. At this time the hemoglobin was 10 gm., and the white-cell count 7200, with 76 per cent neutrophils, 2 per cent young polymorphonuclears and 1 per cent blast forms. A blood culture revealed no growth. A few petechiae appeared over the trunk and extremities. On the eighth hospital day the urinary output began to increase, but the nonprotein nitrogen continued to rise, and a to-and-fro friction rub was then heard over the anterior chest, being loudest over the second and third interspaces on the left. By the ninth hospital day the erythematous rash had faded considerably. She became dyspneic and drowsy, and twitchings occurred at intervals of one second. On the thirteenth hospital day the nonprotein nitrogen had risen to 200 mg. per 100 cc. A platelet count at this time was 58,000. The urine gave a ++++ test for albumin, and the sediment contained 50 red blood cells and 6 white blood cells per high-power field. A swelling developed over the left parotid region. On the fifteenth hospital day the nonprotein nitrogen was 280 mg. per 100 cc. The patient was comatose and exhibited choreiform movements. A uremic frost appeared on the forehead and lips, and she died later that day.

Differential Diagnosis

Dr. Alfred Kranes: Have you any idea what form this patient's sensitivity took? Was it asthma?

Dr. Marian Ropes: It was simply sneezing, with no real asthma.

Dr. Kranes: We are faced with the ever-recurrent problem of trying to predict the histologic picture of a kidney in a patient who obviously died of renal insufficiency and uremia. By and large, that is not likely to be a very accurate clinical exercise, but there is no reason why we should not keep trying. In this case we are limited, it seems to me, to consideration of only the acute forms of renal disease, since this patient's illness lasted exactly one month — unless one wants to make the assumption, hardly justified by the facts given here, that this represents an acute exacerbation of some chronic renal disease. From the information available there is no reason to think that this patient had pre-existing renal disease. The original urine examination, with a specific gravity of 1.022, indicates good function of the kidneys, although no other renal-function tests are given. So I will limit myself to a discussion of certain types of acute, rapidly fatal kidney disease.

We can eliminate from our discussion any of the acute poisonings such as mercury, arsenic or carbon tetrachloride since there is no reason from the history why we should consider them seriously. The most common acute renal disease that will produce this type of picture is acute glomerulonephritis, and there are many parts of this picture that can be well explained by such a diagnosis. Certainly, the hematuria, the oliguria, the pulmonary edema that developed and the eventual uremia and death are readily explainable on this basis. However, several aspects of the picture are a bit unusual. In the first place, nothing is said about the finding of any casts in the urine, although they may have been present. One would expect a patient with acute glomerulonephritis to have a fair number of casts in the urine.

Dr. Walter Bauer: She had frequent granular casts on one specimen only.

Dr. Kranes: One would expect more than that. We are given only one blood pressure reading of 120 systolic, 68 diastolic. Nothing is said about the subsequent course of this patient's blood pressure. I am assuming that there was no appreciable change, but that assumption may be wrong. If the blood pressure showed no rise, it certainly would be strong evidence against the diagnosis of acute glomerulonephritis. But what bothers me even more about such a diagnosis is the early part of the history: the degree of fever, and the amount of pain in the calves, thighs and joints. Did this patient have much joint pain in the upper as well as the lower extremities?

Dr. Ropes: Not as much in the upper extremities. She definitely had joint pain occasionally over the course of two or three years, usually in the upper extremities. About six or eight months prior to entry she had begun to have cerebral symptoms. There was a definite change in judgment and memory. She had a responsible job, and from being a very efficient person she became relatively inefficient, forgetting things and showing evidence of poor judgment.

Dr. Bauer: She also was fatigued and complained of being tired going upstairs. Dr. Ropes elicited that information from the nurse and secretary some time after admission. The blood pressure never did rise. The highest recorded is 170, and some time later it was only 140 or 150.

Dr. Kranes: A fairly normal blood pressure during the development of renal insufficiency is evidence against the diagnosis of glomerulonephritis. As I have just stated, what disturbs me more than either the absence of casts or the elevation of blood pressure is the fever and peripheral discomfort that she had. Fever, of course, is not an uncommon ac-

companiment of glomerulonephritis, but fever of this degree and muscle and joint pains of this degree are not common symptoms of glomerulonephritis.

Dr. Bauer is showing me the chart, which indicates fever in the beginning, gradually coming down to normal. Perhaps the glomerulonephritis, if present, was a complication of some other acute infectious process. What that may have been, I certainly have no idea. There is no evidence on which to localize any type of acute infection. To be sure, during the latter part of the illness she developed a pericardial friction rub, but I am interpreting that as the type of fibrinous pericarditis that so often develops in the terminal stages of uremia. The swelling over the parotid area was a terminal, purulent parotitis in all probability. Whether she had subacute bacterial endocarditis and a complicating nephritis as a result is difficult to say. I am not able, on the evidence given here, to make a diagnosis of subacute bacterial endocarditis.

The presence of fever, pain and renal disease raises the question of acute pyelonephritis. The urinary sediment is not very helpful in establishing such a diagnosis. If this were pyelonephritis, one would have to assume that there was pre-existing renal disease. An acute attack would not be expected to produce death so rapidly.

We come now to a discussion of the possible role of sulfonamides in this patient's terminal illness. I would like to ask how certain we can be that she received no sulfonamides before coming to the hospital.

Dr. Ropes: I am very sure that she had not received any.

Dr. Kranes: That is important because there is some evidence on admission to the hospital that this patient already had renal disease as evidenced by the albuminuria and the hematuria. The picture as described indicates that sulfonamides may have played some role in the development of the subsequent renal insufficiency, since the urinary output seems to have diminished following their administration. If the history is accurate, and we have to believe it is, I do not see how we can incriminate the sulfonamides as underlying this renal disease. They may have aggravated it.

The usual types of lesions produced by sulfonamides, as you know, are precipitation in the renal tubules of sulfonamide crystals and the rapid development of oliguria. That is a possibility. Another type of lesion is lower-nephron nephrosis, which, unless this patient had previously been given sulfonamides, seems improbable. The third type of lesion produced by sulfonamides is a periarterial lesion, periarteritis nodosa, first described by Rich* and subsequently confirmed by other workers on clinical cases. On the whole, I would be inclined to disregard the role of sulfonamides in this particular patient, since she had renal disease before they were given.

We know that periarteritis can exist in the absence of sulfonamide administration. It is a disease that has to be seriously considered in this patient. I see nothing in the history as given here that would be against such a diagnosis. The muscular and joint pains, the fever and the renal disease all fit that diagnosis. One thing that bothers me about such an explanation is the short course of this patient's illness. Dr. Ropes has added further data indicating that this patient had not been in good health for six months. That would fit in very well with the diagnosis of periarteritis. Of course, all the features of the disease were not present here. There was no eosinophilia, but that is not too disturbing. There was no asthma.

In this regard I think it might be worth speculating about the possible role of sulfonamides, if this patient does turn out to have had periarteritis nodosa. I do not believe Dr. Mallory will be able to answer that, but it is interesting to speculate about it. Given a patient with periarteritis nodosa, what would happen if sulfonamides were given, a drug we know is capable of producing the disease in a sensitized patient? I do not know. It does seem from the description that the disease might have been accelerated by the administration of sulfonamides, but I do not see how we can answer the question.

What I have said about periarteritis applies equally well to another disease — acute disseminated lupus. The differential between the two I do not believe I can make clinically. When I say "periarteritis nodosa" I mean that the patient might also have had the renal lesions of disseminated lupus, although pathologically they are quite different. The skin rash, joint pains and fever and even the pericardial friction rub, although it is much more likely to have been a uremic pericarditis, might have been evidences of disseminated lupus. We have seen

*Rich, A. R. Role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.* 71:123-140, 1942.

cases that clinically seemed to have one disease and pathologically the other.

Finally, I think one other disease should be mentioned, although it is pretty far-fetched. I am sure those who saw the patient will think it absurd. But as I get the picture from the description in the record of the initial symptoms in her legs — pain, stiffness of the calf and tenderness, the possibility occurred to me that the patient had an acute thrombophlebitis, although nothing further is said about it. If that were so, one might easily conceive of this process extending up into the iliac veins, possibly to the vena cava, and if it extended up far enough, it might occlude the mouths of both renal veins or extend into the renal veins causing hemorrhagic infarction of both kidneys and renal insufficiency. I realize it is a rare and unusual possibility but, as the picture is given here, not an impossible one.

In summary, then, I think we have to consider only three general possibilities: glomerulonephritis, one of the lesions produced by sulfonamides and periarteritis nodosa. Of these three possibilities it seems to me that the least objectionable one would be periarteritis nodosa. So I shall guess that that was what this patient had.

Dr. Tracy B. Mallory: I take it that the x-ray films are not contributory?

Dr. Stanley M. Wyman: No, there is just a question of pleural reaction at the left, which may perhaps tend to implicate the pleura rather than the pericardium. Whether that is a help, I do not know.

Dr. Kranes: I do not see how it casts any light on the renal problem.

Dr. Bauer: The following note shows what we thought about this woman at the time of entry and what we believed she might be suffering from, although we would be the first to admit that we were not too certain of the exact nature of the disease (this was written six days after admission):

When I first saw this patient I thought she was suffering from meningococcemia manifested by fever, headache, rash and arthritis. Sulfadiazine was started on the same day (3 gm.). After a total of 7 gm. of sulfadiazine, oliguria was evident, although there was no history of previous ingestion of any type of sulfonamide. On the same day she received 2200 cc. of physiologic saline solution as well as two ampules of sodium racemic lactate. This added sodium intake was sufficient to increase the patient's blood volume to a point where obvious signs of congestive failure appeared. With the discontinuance of sulfadiazine, penicillin (400,000 units every twenty-four hours) therapy was instituted. Forty-eight hours after the start of sulfadiazine and twenty-four hours after penicillin the temperature fell, and the leukocyte count dropped from 13,000 to 6000. Up to today I felt reasonably certain that the patient had had a bacterial infection that had responded to specific treatment, but that she had the misfortune of developing a sulfonamide nephrosis and congestive failure by increasing her blood volume at a time when she had oliguria. The oliguria has improved, and the patient is now able to take fluids much better.

This morning the clinical picture resembles that seen on the day of entry, except that the rash is not as marked and the vesicular lesions on the chest are pruritic. Could the reappearance of these findings be related to the barbiturate she received last night? Is she sensitive to other agents than sulfonamides? For the time being it seems unwise to use any type of sedative.

At the moment I am unable to make a satisfactory diagnosis. I am still inclined to believe we have been dealing with a patient who had a bacterial infection, who is sensitive to sulfonamides and perhaps other drugs. There is little to suggest either rheumatic fever or rheumatoid arthritis. We must still entertain the possibility of subacute bacterial endocarditis, lupus erythematosus and periarteritis nodosa. Treatment for the time being should be good nursing and a minimum of drugs.

Subsequent to that Dr. Ropes obtained additional information that the patient had not been feeling well for at least six months. Frankly, I must say that up to the time she died I did not know for certain what she was suffering from, but was inclined to believe it was more likely periarteritis nodosa or lupus erythematosus disseminatus. The last we heard from the Pathology Department they were not certain, but perhaps we will see.

Clinical Diagnoses

Periarteritis nodosa.
Uremia.

Dr. Kranes's Diagnosis

Periarteritis nodosa.

Anatomical Diagnoses

Lower-nephron nephrosis.
Pericarditis, acute.
Myocarditis, focal.
Pneumonitis, interstitial.
Bronchopneumonia, terminal.
Hematopoiesis of spleen.

Pathological Discussion

Dr. Mallory: The Pathology Department is far from certain about this case. We are able to name

the renal lesion, for what that is worth. She had a severe lower-nephron nephrosis, with pigment casts in many of the distal tubules and the usual degenerative changes in the ascending limbs of Henle's loops, the interstitial inflammation and thrombi of the large renal veins, which are all characteristic of this lesion. Beyond that we are in the realm of pure speculation. We found a fibrinous pericarditis. Microscopically, there was an extensive, focal myocarditis and also interstitial pneumonitis. There were a few granulomatous lesions in the portal areas of the liver. A complete surprise, since there was nothing to suggest a blood dyscrasia, was the presence of many foci of hematopoiesis in the spleen. The bone marrow was very hyperplastic in both red-cell and white-cell series. There was acute arteritis and phlebitis in a small tab of mesenteric fat in one of the epiploic appendixes, but no other vascular lesions elsewhere in the body. The joints were normal, as were the heart valves. None of the lesions in the heart were characteristic of Aschoff bodies or other stigmas of rheumatic fever. We found nothing to substantiate a diagnosis of rheumatic fever, rheumatoid arthritis, lupus erythematosus or periarteritis nodosa. This type of case makes one think very seriously of the possibility of some of the rare infections — histoplasmosis or toxoplasmosis — but a number of us in the laboratory have searched the sections repeatedly and are unable to find any organisms of such character.

I am also unable to explain the development of the lower-nephron nephrosis in this case. I agree with Dr. Kranes that the history strongly suggests that the patient had renal disease before she had sulfonamides, and I do not believe we can attribute the lesion to sulfonamide therapy. The possibility that the lesion develops following the sensitization to other drugs has been raised on a few occasions. I have seen a case in which it was attributed to streptomycin, though on flimsy evidence. I have never heard of it following aspirin, which is the only drug mentioned in the immediate past history.

DR. BAUER: In retrospect, I wish we had never given sulfonamides because the sequence of events that ensued following the administration of the sulfonamides was perhaps coincidental but, nevertheless, very impressive. Would you agree to that, Dr. Ropes?

DR. ROPES: Yes, it was very impressive.

DR. BAUER: If I had to do it again, I would never have employed sulfonamides. The patient's brother was a physician, her sister was a teacher and very intelligent, and on more than one occasion we tried hard to get a history from them of the previous taking of sulfonamides but could not. Whether that rules out sulfonamide sensitivity, I do not know.

DR. JACOB LERMAN: It seems to me that it is easy to get sensitivity to sulfonamides by the use of ointments and nose drops that almost every doctor gives in his practice every day.

DR. MALLORY: Yes, there was one case that, as far as we could make out, was sensitized by a sulfonamide chewing gum.

The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.
Joseph Garland, M.D., Editor

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.
Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. James M. Faulkner, M.D.
Robert M. Green, M.D. Carroll B. Larson, M.D.
Dwight O'Hara, M.D. Francis D. Moore, M.D.
Fletcher H. Colby, M.D. C. Stuart Welch, M.D.
Robert L. Goodale, M.D. Vernon P. Williams, M.D.
Chester M. Jones, M.D. Benjamin Castleman, M.D.
Harvey R. Morrison, M.D. Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS, *including those concerning classified advertising but not those regarding other advertising*, should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE (*except for classified advertising*): Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

"I HAVE CANCER"

As ALREADY noted in these columns, April is the month in which interest in the control of cancer is brought to its sharpest focus. Consideration has been given to heart-disease month, and the nation is currently passing through cancer-control month, mindful of the 1949 goal of $14,500,000 in donations to be achieved; according to a recently developed national tradition, the country is in fact encountering a succession of chronological periods especially consecrated to unusually worthy causes.

Of the hazards to life that mankind is now constantly combating with better equipment and with greater success than ever before, heart disease and cancer offer a significant comparison. Each is acknowledged as particularly important among the diseases of later life, each, in certain aspects, being evidence of the inevitable wearing out of the human machine. Each is of increasing importance as a cause of death, largely because of the considerable control that has been acquired over the diseases of early life.

Here, however, the similarity ends. Degenerative diseases of the heart are accepted almost as a badge of merit. They are considered to be the penalty of industrious application to one's duty and the discharging of a personal debt to society, with interest. Like ulcer, they represent a wound stripe of modern civilization. Cancer, ominous and mysterious, inspires a terror that the conception of heart disease seems to lack. It still implies a portentous degree of finality, as if the knell were already struck, the tolling of the bell begun.

The reasons for these differences in viewpoint are obvious. Heart disease warns of its encroachment on the patient's health, and good behavior may postpone indefinitely the final accounting. The idea of a fighting chance for the prolongation of life, with reasonable activity and comfort, is almost always present. Cancer, on the other hand, is a fifth column that may have infiltrated beyond hope of eradication before it is discovered. The medical profession itself, with the label of "malignancy" that it has applied to cancer, has helped to emphasize the horror associated with it.

No enemy can be hopefully opposed that is allowed to entrench itself in the shadows. Implicit in the campaign against cancer is the bringing of it into the open. The lesson must be reaffirmed that cancer is a disease that can be combated and frequently conquered if early diagnosis is permitted. Many new agents both of diagnosis and of treatment are being brought to bear against it. Reticence is one of its most powerful allies.

The *Reader's Digest* for November, 1948, contains an article by a newspaper editor, entitled "I Have Cancer." The point of this courageous story, by one whose condition was apparently discovered too late for successful treatment, is that "the paralyzing hush hush that surrounds cancer" must be dispelled. In the interest of early diagnosis with its increased

opportunity for cure; for the sake of encouraging the patient with cancer to lead as normal a life as possible, the disease must be accepted simply as another of the hazards that encompass life, and that man is slowly conquering.

POTASSIUM IODIDE AND STREPTOMYCIN FOR TUBERCULOSIS

Most of the clinical experience with the streptomycin treatment of pulmonary tuberculosis has indicated that this antibiotic is effective against the acute exudative lesions and that little or no benefit may be expected in the chronic fibroid or fibrocaseous types of pulmonary lesions, in which the antibiotic may not have adequate access to the organism. In an attempt to create experimentally a more favorable opportunity for streptomycin to act on such lesions Woody and Avery[1] have utilized the well known clinical observation that the administration of iodides causes tubercle bacilli to appear in the sputum of patients with pulmonary tuberculosis in whom the organisms were previously absent.

The rationale for their experiments is based upon the observations of Jobling and Petersen[2] that iodides may act on the tuberculous lesion in two ways: it may combine with the unsaturated fatty acids of the tubercle bacilli and neutralize their ferment-inhibiting properties; the enzymatic action that then occurs within the areas of caseation liberates the bacilli from these foci. In addition, the iodides facilitate the solution and absorption of the caseous material, thus exposing the bacilli that might otherwise be inaccessible to the agents.

After determining that potassium iodide has no effect on the antibiotic properties of streptomycin, Woody and Avery set up controlled experiments in guinea pigs to determine whether potassium iodide in combination with streptomycin would be more effective than streptomycin alone against a virulent tuberculous infection. The early results seem to justify their expectation. In their first experiment, treatment was started three weeks after infection, and all animals were killed seven weeks after infection. The control animals and those receiving only potassium iodide all showed heavy tuberculous infection; some of the animals treated with streptomycin alone demonstrated a spread of infection to the organs during treatment while the organs of the animals treated with the combination of potassium iodide and streptomycin were entirely free of infection on gross examination. In a second experiment in which animals were observed for fifteen weeks after infection, all the control animals died; 6 of 13 streptomycin-treated animals died, whereas only 2 of 14 given streptomycin and potassium iodide died.

These results seemed impressive enough to stimulate clinical trials of this type of therapy, which are now in progress. It should be borne in mind, however, that the treatment is not without some risk. If potassium iodide causes a breakdown of the tuberculous lesion and if streptomycin treatment results in the rapid appearance of streptomycin-resistant organisms, as is usually the case, one defense of the body has been eliminated. In some of the patients in whom the resistant organisms appear, the lesions may then be expected to progress more rapidly after this treatment, and streptomycin may then be without effect and potentially harmful.

References

1. Woody, E., Jr., and Avery, R. C. Combined effect of potassium iodide and streptomycin on established tuberculosis in guinea pigs. *Science* **108**:501, 1948.
2. Jobling, J. W., and Petersen, W. Study of ferments and ferment-inhibiting substances in tuberculous caseous material. Studies on ferment action. XII. *J. Exper. Med.* **19**:383-397, 1914.

"HONOUR A PHYSICIAN"

A special convocation was held on Sunday afternoon, January 23, at Hobart and William Smith Colleges to mark the one hundredth anniversary of the graduation from Geneva (now Hobart) College of Elizabeth Blackwell, the first woman to receive a degree in medicine. Ten leading women physicians from the United States and Canada and one each from England and France were cited by Dr. Alan W. Brown, president of the Geneva Colleges, in the name of Elizabeth Blackwell; the response was by Dr. Priscilla White, of Boston.

New England received its share of the honors of the day, for of the ten American and Canadian physicians selected by the deans of the medical schools of the two countries, four are natives of New England.

Dr. Martha May Eliot, associate chief of the United States Children's Bureau, is also the first woman to have been president of the American Public Health Association. A native of Dorchester, Massachusetts, she graduated from Johns Hopkins University School of Medicine in 1918.

Dr. Alice H. Hamilton, of Hadlyme, Connecticut, professor emeritus of Industrial Medicine at Harvard, was the first woman to be a member of the Harvard faculty. A graduate of the University of Michigan Medical School in 1893, she was cited for her contributions to industrial toxicology.

Dr. Helen B. Taussig, born in Cambridge, Massachusetts, received her degree in medicine at Johns Hopkins University School of Medicine, where she is now associate professor of pediatrics. She is the winner of many awards for her work with Dr. Alfred Blalock in studying and developing operative technics for the correction of congenital cardiac defects.

Dr. Priscilla White, a graduate in 1923 of Tufts College Medical School, is a clinical teacher at that school, a practicing physician in Boston and a member of the staff of the New England Deaconess Hospital. She is, in the words of Dr. Brown, "known throughout the land for her research in the field of diabetes with special reference to diabetic children and mothers. . . . Representing here today the women doctors of the world, we are proud to cite her for her own service to medicine and medical research."

The *Journal* takes pride also in honoring these four women, and with them their illustrious colleagues: Dr. Florence R. Sabin, of Denver, Colorado; Dr. Gerty T. Cori, of Webster Groves, Missouri; Dr. Helen V. McLean, of Chicago, Illinois; Dr. Margaret D. Craighill, of Topeka, Kansas; Dr. Helen MacMurchy, of Toronto, Canada; Dr. Elise S. L'Esperance, of New York; Dr. Helen M. M. Mackay of London, England; and Dr. Thérèse Bertrand Fontaine, of Paris, France.

TRANSCUTANEOUS JET PROPULSION

Those Americans have invented a new gadget, described first by Hingson and Hughes[1] in 1947, employed by Hirsh and his co-workers[2] in 1948 and commented on not unfavorably, although with caution, in a recent issue of the *British Medical Journal*.[3] It consists of a machine that can propel, painlessly and at a speed perhaps only slightly faster than sound, a therapeutic or immunizing substance into, through and beyond the apparently unbroken epidermis.

The damyankees, long considered technical masters of the subject, have discovered a new way of getting under people's skin.

The Microjet or Hypospray is based on the principle that a fine, high-pressure jet can pierce the skin, with little if any pain. In its practical application, the material to be injected is placed in a metal ampule (or Metapule) with a capacity of 0.25 cc. The Metapule, shaped like a blunt-nosed bullet, has an orifice 0.003 inches in diameter in the rounded tip. The butt end is stoppered with a rubber plug; the Metapule is locked into the front end of the machine, and, when all is ready, a high-tension spring attached to a plunger is released by pressure on a button.

When this occurs "The plunger explodes against this rubber stopper which forces the material out of the Metapule and through the skin as a fine spray. The material is deposited subcutaneously and intramuscularly to depths varying from 0.2 to 2 cm. depending on the tension of the spring and the site of injection."[2] The jet exerts a pressure of 2300 to 3500 pounds per square inch on the skin, "which has no alternative but to let it through."

Hingson and Hughes find that blood concentrations of penicillin obtained with the Hypospray are higher and more prolonged than when needle and syringe are used, probably because parts of the solution are deposited subcutaneously as well as intramuscularly.

The warning is issued that a frontal attack must be made against the taut skin. If the skin is wet or the nose of the ampule is not in close contact with it or is tilted, the injection produces a cut or a blister.

This instrument is said to eliminate the fear incident to injection by needle and syringe.

References

1. Hingson, R. A., and Hughes, J. G. Clinical studies with jet injection. New method of drug administration. *Current Researches in Anesth. & Analg.* **26**:221-230, 1947.
2. Hirsh, H. L., Welch, H., Milhoff, B., and Katz, S. Administration of penicillin and streptomycin by means of hypospray apparatus (jet injection); absorption, toxicity, and stability. *J. Lab. & Clin. Med.* **33**:805-810, 1948.
3. Annotation. Jet injection. *Brit. M. J.* 2:830, 1948.

MASSACHUSETTS MEDICAL SOCIETY

POSTGRADUATE LECTURE COURSE

The April 25 session of the Postgraduate Lecture Course will be held in the New Lecture Hall, Cambridge, instead of at Sanders Theater.

The New Lecture Hall is located across Kirkland Street from Sanders Theater, at the corner of Kirkland and Oxford streets.

A.M.A. ASSESSMENT

The following letter will, I am sure, interest many fellows of the Society:

H. Quimby Gallupe, M.D.
8 Fenway
Boston 15, Massachusetts

Dear Dr. Gallupe:

Enclosed is my check for special assessment.

I am impressed with the sincerity and efforts of the Society officers to meet the issues squarely. I also feel that the critical efforts through the town meetings of doctors has been effective in guiding the efforts that reached Chicago through our local organization.

From here on it is up to the younger members of the American Medical Association to attend the district meetings and see that constructive proposals are carried upward through our organization.

Sincerely yours,
EARLE M. CHAPMAN, M.D.

H. QUIMBY GALLUPE, *Secretary*

DEATHS

BAILEY — Florence Bailey, M.D., of Lawrence, died on December 24. She was in her seventy-second year.

Dr. Bailey received her degree from College of Physicians and Surgeons, Boston, in 1903.

CRITTENDEN — Samuel W. Crittenden, M.D., of Wakefield, died on March 27. He was in his ninety-third year.

Dr. Crittenden received his degree from Dartmouth Medical School in 1898. He was a member of the New England Society of Psychiatry.

His widow survives.

HUGHES — John Hughes, M.D., of Pittsfield, died on February 12. He was in his sixty-seventh year.

Dr. Hughes received his degree from University of Vermont College of Medicine in 1905. He was associate medical examiner of Berkshire District and was a member of the staffs of St. Luke's and Pittsfield General hospitals. He was a former councilor of the Massachusetts Medical Society.

His widow, two daughters, five grandchildren and his mother survive.

WARREN — Hobart E. Warren, M.D., of Palm Beach, Florida, died on March 17. He was in his eighty-first year.

Dr. Warren received his degree from Harvard Medical School in 1894. He was a former member of the Massachusetts Medical Society and a fellow of the American Medical Association.

His widow and a daughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The May schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CONSULTANT
Salem	May 2	Paul W. Hugenberger
Haverhill	May 4	William T. Green
Lowell	May 6	Albert H. Brewster
Greenfield	May 9	Charles L. Sturdevant
Gardner	May 10	Carter R. Rowe
Brockton	May 12	George W. Van Gorder
Springfield	May 17	Garry deN. Hough, Jr.
Pittsfield	May 18	Frank A. Slowick
Worcester	May 20	John W. O'Meara
Fall River	May 23	David S. Grice
Hyannis	May 26	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

INFANT MORTALITY, 1947

The infant mortality rate in 1947 was the lowest recorded in the United States, according to a release from the National Office of Vital Statistics of the Public Health Service, Federal Security Agency. The rate in that year fell from the 1946 figure of 33.8 infant deaths per thousand live births, to 32.2. It was expected that the decline would continue to a rate of 31.8 in 1948.

The five leading causes of infant deaths in 1947 and the rates for each are: premature birth, 11.1; congenital malformation, 4.6; pneumonia and influenza, 3.6; birth injury, 3.5; and asphyxia and atelectasis, 1.6.

CORRESPONDENCE

MORE ON THE CARE OF THE PATIENT

To the Editor: I fully agree with Dr. Henry F. Howe's letter, "The Care of the Sick" in the March 10 issue of the *Journal*. I should, however, like to add a word of advice, and it is this: every medical graduate should have, besides an internship, an externship. Every physician, when he first starts out to practice for himself, knows the clumsy and embarrassing situations he frequently finds himself in. He lacks bedside manners; he does not have the proper approach toward either the patient or his immediate family. He is unable to advise on home nursing care — (as an intern he seldom, if ever, had to make such decisions). The general practitioner, not infrequently, has to use his resourcefulness in improvising gadgets that the intern has no need for. No lectures, books or films can make one adept in doing things, and only by actually doing things can one learn to do them well. To solve these as well as many more unforeseen problems that arise, I suggest that every young physician, after completing his internship, should be apprenticed for a year to a busy country general practitioner. The actual practical experience thus obtained would benefit not only the patient, but much more so the physician beginner. He would acquire the skill in diagnosing correctly the largest number of his cases without having to resort to the so-called instruments of precision (most of them are not) and would thus save precious time. In a word, he would develop the self-confidence that goes to make a good physician.

MOSES AKIN, M.D.

Ellenville, New York

SIGNIFICANT FIGURES

To the Editor: It should be of interest to all the readers of the *Journal*, including the proponents of compulsory health insurance, to know about the recent results of a poll taken of the members of the Worcester District Medical Society. The results of this poll, incidentally, were printed in the *Secretary's Letter* (of the American Medical Association), No. 99, March 14, 1949.

In response to the poll, in which they were asked to answer whether they were in favor of or opposed to compulsory health insurance as proposed by Senate Bill S. 5, 75 per cent of the members took the time to answer — a remarkable number of returns, particularly when doctors are concerned. Ninety-seven per cent were opposed to compulsory health insurance, and only three per cent were in favor of it. Out of 330 returns, 318 were opposed, 11 were in favor and 1 was undecided.

This should be the answer for those who use the word "many" with no facts or figures to back it up. When the minority groups make a statement that many doctors favor Government medicine, they should be shown that when transposed into percentages, 3 per cent looks a lot less than the word many.

N. S. Scarcello, *Chairman*
Public Relations Committee
Worcester District Medical Society

Worcester, Massachusetts

REGARDING GROUP PRACTICE

To the Editor: The title of the fine editorial in support of Senator Chapman's Local Public Health Units Act of 1949 (S. 522), which appeared in the February 24 issue of the *Journal*, caught my eye because of my interest in still "*another* bulwark against socialized medicine" — that is, prepaid group practice.

In 1947 Hunt and Goldstein, in the *New England Journal of Medicine* (**237**:71-77 and 719-731, 1947) and in the *Journal of the American Medical Association* (**135**:904-909, 1947, and **136**:857-861, 1948), reviewed the services, organization, administration and professional opinion of 368 group-practice plans. Eight of the 368 were in New England, and 2 were in Massachusetts. None of the 8 were on a prepaid basis.

In May, 1948, the representatives of the American Medical Association at the National Health Assembly in Washington agreed ". . . that voluntary prepayment group health plans . . . offer to their members the best of modern medical care" and that "the people have the right to establish voluntary insurance plans on a co-operative basis." The more recent twelve-point program, as pointed out in the *Journal of the American Medical Association* (**139**:529, 1949), implies accession to these principles.

At the Massachusetts Health Conference held last month in Boston, the panel on medical-care costs and methods reaffirmed the advantages of group-practice prepayment plans, and encouraged their use, as noted in the editorial entitled "Massachusetts Five-Year Plan" in the March 10 issue of the *New England Journal of Medicine*. However, debate was largely between the proponents of the two extreme points of view — that is, improved coverage within the *status quo* and national health insurance. Consequently, the acknowledgedly best compromise measure yet proposed received little attention.

The response of communities that have been in urgent need of improved medical care and have also been afforded friendly and encouraging legislation and professional co-operation confirms the practical applicability of such plans. Since Texas passed its Rural Co-operative Health Plan bill in 1945, 50 consumer-sponsored medical-plan charters have been granted and 17 hospital clinics have been established. In Wisconsin enabling legislation enacted July, 1947, has been followed by at least 5 co-operative plans and a co-operative hospital opened in Wild Rose, Wisconsin, little more than a year later.

The American Medical Association argues that a broad federal health program at present is premature in the face of the lack of sound experience and experimentation. It has voiced its readiness to accept the types of medical service plans that, although voluntary, can afford the experience needed to provide better medical care at a minimum cost to medically marginal communities. Those communities may be either sparsely settled areas or of marginal income populations. In either case, given the opportunity, many communities are ready and eager to experiment in this field of medical economics.

An American Medical Association questionnaire of doctors in the armed services indicated that 54 per cent preferred group practice. All, of course, had been experiencing a sort of prepaid group practice while in the service. It seems reasonable that these two groups, doctors and consumer patients, might with encouragement from national and local medical associations get together on a mutually satisfactory basis.

Therefore, it is to be hoped that some of the progressive steps outlined in the twelve-point program will be furthered by the *active* support of organized medicine in the removal of restrictive legislation and its positive encouragement of participation by doctors in voluntary medical-care plans of all types compatible with high standards of medical science and ethics.

Donnell W. Boardman, M.D.

Maynard, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

An Index of Treatment: *By various writers.* Edited by Sir Robert Hutchison, Bt., M.D., LL.D., F.R.C.P., consulting physician, London Hospital and Hospital for Sick Children, Great Ormond Street. Assisted by Reginald Hilton, M.A., M.D., F.R.C.P., physician to St. Thomas's Hospital, consulting physician, Epsom Hospital, and consulting physician and cardiologist, Wembley Hospital. Thirteenth edition, revised. 4°, cloth, 972 pp., with 99 illustrations. Baltimore: Williams and Wilkins Company, 1948. $17.00.

This treatise was first published in 1907, and this edition has been thoroughly revised, and the subject matter brought up to date. The text is the joint work of seventy-four contributors. The material is arranged alphabetically, and there is a supplemental comprehensive index of sixty pages. The type and paper are good, and a light paper is used to advantage in such a large volume. The number of editions speaks well for the soundness of the work, and it should prove valuable to the practicing physician and is recommended for all medical libraries as a standard reference work.

Urology for Nurses. By Oswald S. Lowsley, M.D., director, Department of Urology (James Buchanan Brady Foundation), New York Hospital, consulting urologist, St. Clare's Hospital and Hospital for the Ruptured and Crippled, New York City, Monmouth Memorial Hospital, Long Branch, New Jersey, Englewood Hospital, Englewood, New Jersey, St. Luke's Hospital, Newburgh, New York, St. Agnes Hospital, White Plains, New York, and Norwalk Hospital, Norwalk, Connecticut; and Thomas J. Kirwin, M.D., attending surgeon, Department of Urology (James Buchanan Brady Foundation), New York Hospital, visiting genitourinary surgeon, New York City Hospital, consulting urologist, Coney Island Hospital, Monmouth Memorial Hospital, Long Branch, New Jersey, Benedictine Hospital, Kingston, New York, and St. Vincent's Hospital, Montclair, New Jersey. Second edition. 8°, cloth, 687 pp., with 130 illustrations by William P. Didusch. Philadelphia: J. B. Lippincott Company, 1948. $6.00.

The authors have revised this second edition of their manual for nurses, first published in 1936, to bring it up to date. Some chapters have been completely rewritten, and cystoscopy and radiography have been brought together in one chapter. Many illustrations have been added. A glossary of urologic terms and a good index conclude the text. The book is well published and should prove useful as a compendium of the subject.

Principles Governing Eye Operating Room Procedures. By Emma I. Clevenger, R.N., supervisor, eye operating room, New York Eye and Ear Infirmary, New York City. 8°, cloth, 215 pp., illustrated. St. Louis: C. V. Mosby Company, 1948. $5.50.

This manual outlines the procedures for the operating room of an eye hospital. It discusses the care and handling of instruments and equipment, sutures, dressings, rubber gloves, linens and drugs. A large part of the book is devoted to a description of setups for various eye operations. It is based on experience gained in the New York Eye and Ear Infirmary. The books should prove useful to eye surgeons and hospital libraries.

"Elective Alimentary Rest" and the Elimination of So-called "Paralytic Ileus" after Abdominal Operations. By V. J. Kinsella, M.B., Ch.M.(Syd.), F.R.C.S. 8°, paper, 35 pp., with illustrations. Sydney, Australia: Australasian Medical Publishing Company, Limited, 1948. 3 shillings.

This pamphlet brings together a number of papers originally published in periodicals by the author. The author describes his postoperative plan, especially in cases of appendicitis, in which no solids or solid-forming liquids are given for six days after the operation. A diet for the six days is given, consisting of liquids, except milk, and soft foods. Aperients, enemas, hypodermic injections for retention of urine and drugs, such as pituitrin and eserine, are not permitted. The author claims excellent results for his treatment based on 344 cases of acute appendicitis treated during a period of twelve years.

General Endocrinology. By C. Donnell Turner, Ph.D., associate professor of zoology, Northwestern University. 8°, cloth, 604 pp., with 163 illustrations. Philadelphia: W. B. Saunders Company, 1948. $6.75.

This textbook is designed for beginning students who are concentrating on experimental biology and is based on the lectures given at Northwestern University. The subject is approached from the experimental rather than the clinical point of view. The material is well organized and bibliographies are appended to the various chapters. A good index concludes the volume. The publishing is excellent. The book is recommended for all medical libraries and to all students interested in the subject.

NOTICES

ANNOUNCEMENT

Dr. George P. Sanborn announces that he has resumed the practice of medicine at Hotel Eliot, 370 Commonwealth Avenue, Boston.

HAMPDEN DISTRICT MEDICAL SOCIETY

The annual meeting of the Hampden District Medical Society will be held at the Longmeadow Country Club, Tuesday, April 26, and *not* at the Highland Hotel as formerly announced.

Cocktails will be served at 6:00 p.m.

The speaker of the evening will be Dr. Douglas T. Davidson, whose subject will be "Convulsive Disorders."

94TH INFANTRY DIVISION LECTURES

The 94th (Bay State) Infantry Division is sponsoring a series of monthly lectures by prominent physicians in their respective specialties. The third lecture will be held in Room 720, United States Post Office and Court House, Post Office Square, Boston, on Wednesday, April 27, at 8 p.m.

Dr. Morton Brown will speak on the subject "Physiologic Approach to Congestive Heart Failure."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit. Excellent films will also be shown during this period.

NEW ENGLAND HEART ASSOCIATION

The annual Henry Jackson Lecture, under the auspices of the New England Heart Association, will be given by Dr. Harold G. Wolff, professor of medicine and associate professor of psychiatry, Cornell University Medical College, and attending physician, New York Hospital, at the Boston Medical Library, 8 Fenway, Boston, on Monday, May 9, at 8:15 p.m. His subject will be "Life Stress and Cardiovascular Disorders."

A short business meeting will precede the lecture. Interested physicians and medical students are invited to attend.

AMERICAN PSYCHIATRIC ASSOCIATION

The one hundred and fifth annual meeting of the American Psychiatric Association will be held at the Windsor Hotel, Montreal, Quebec, May 23–27.

The question of the reorganization of the Association, which has been under consideration for several years, will come up for further discussion at this meeting, and an unusually large attendance is expected.

SOCIETY MEETINGS AND CONFERENCES

April 23. Massachusetts Association of Medical Technologists. Page 628, issue of April 14.

April 26. Greater Boston Medical Society. Page xv, issue of April 14.

April 26. Hampden District Medical Society. Notice above.

April 27. 94th Infantry Division Lectures. Notice above.

April 28. Massachusetts Psychiatric Society and Boston Society of Psychiatry and Neurology. Page xv, issue of April 14.

April 30. Long Island College Alumni Association. Page 528, issue of March 31.

May 2–26. Consultation Clinics for Crippled Children in Massachusetts. Page 666.

May 4. New England Obstetrical and Gynecological Society. Springfield Country Club, Springfield.

May 5. Suffolk Censors' Meeting. Page 276, issue of February 17.

May 5. Roswell Park Lecture and Medal. Page 588, issue of April 7.

May 7. New England Society of Anesthesiologists. Page 401, issue of March 10.

May 9. New England Heart Association. Notice above.

May 10. Harvard Medical Society. Lower Out-Patient Department Amphitheater, Massachusetts General Hospital.

May 12. Chemotherapy of Leukemia and Lymphosarcoma. Dr. William Dameshek. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

May 16–19. American Urological Association. Biltmore Hotel, Los Angeles, California.

May 18–21. Association for Physical and Mental Rehabilitation. Page 401, issue of March 10.

May 25–27. American Psychiatric Association. Notice above.

May 24–26. Massachusetts Medical Society. Annual Meeting. Worcester Memorial Auditorium, Worcester.

May 24–26. Massachusetts Physicians Art Association. Page 588, issue of April 7.

May 26–28. American Goiter Association. Hotel Loraine, Madison, Wisconsin.

May 30–June 3. International Congress on Rheumatic Diseases. Page 800, issue of November 18.

June 1–3. Academy of Neurology. Page 588, issue of April 7.

June 2–5. American College of Chest Physicians. Page 490, issue of March 24.

June 3–5. Christian Medical Society. Page xv, issue of April 14.

June 20–23. Annual Conference of Health Officers and Public Health Nurses. Page xvii, issue of February 3.

June 20–23. American Society of Medical Technologists. Page 528, issue of March 31.

June 30–July 2. American Association of Railway Surgeons. Page 490, issue of March 24.

September 6–10. American Congress of Physical Medicine. Page xii, issue of March 24.

September 28–30. Mississippi Valley Medical Society. Page 1000, issue of December 30.

October 8–15. American Society of Clinical Pathology. Page xiii, issue of March 24.

November 2. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

District Medical Societies

HAMPDEN

April 26. 6:00 p.m. Longmeadow Country Club, Springfield. (Dinner Meeting.) Convulsive Disorders. Dr. Douglas T. Davidson.

(*Notices concluded on page xi*)